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WJI covers a wide range of subjects including: (1) autoimmune diseases such as type 1 diabetes, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, myasthenia gravis, in both humans and animal models of disease, with an interest on aspects including the etiology, pathogenesis, mechanisms of disease induction, maintenance and progression; (2) tumor immunology including immunosurveillance, immunoeediting and immunotherapies in animal models and in humans; (3) clinical immunology in humans and animal models including mechanisms of disease, regulation and therapy and immunodeficiencies; (4) innate immunity including cell subsets, receptors and soluble mediators, complement and inflammation; (5) adaptive immune mechanisms and cells including soluble mediators and antibodies; (6) immune cell development, differentiation, maturation; (7) control mechanisms for immune cells including immune tolerance and apoptosis; (8) immune cell interactions and immune cell receptors; (9) immunological methods and techniques; (10) immune cell activation including cell signaling pathways, biochemical and pharmacologic modulation studies; (11) infection; (12) different modalities of vaccination including gene therapy; (13) hypersensitivity and allergy; (14) transplantation.

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World Journal of Immunology
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Crucial roles of macrophages in the pathogenesis of autoimmune disease

Aya Ushio, Rieko Arakaki, Akiko Yamada, Masako Saito, Takaaki Tsunematsu, Yasusei Kudo, Naozumi Ishimaru

Aya Ushio, Rieko Arakaki, Akiko Yamada, Masako Saito, Yasusei Kudo, Naozumi Ishimaru, Department of Oral Molecular Pathology, Tokushima University Graduate School of Biomedical Sciences, Tokushima 770-8504, Japan

Masako Saito, Department of Human Genetics, Tokushima University Graduate School of Biomedical Sciences, Tokushima 770-8504, Japan

Takaaki Tsunematsu, Department of Pathology and Laboratory Medicine, Tokushima University Graduate School of Biomedical Sciences, Tokushima 770-8504, Japan

Author contributions: Ushio A, Arakaki R, Yamada A, Saito M, Tsunematsu T, Kudo Y and Ishimaru N wrote a paper; Ushio A, Arakaki R, Saito M, Kudo Y and Ishimaru N prepared figures.

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Correspondence to: Naozumi Ishimaru, DDS, PhD, Department of Oral Molecular Pathology, Tokushima University Graduate School of Biomedical Sciences, 3-18-15 Kuramoto, Tokushima 770-8504, Japan. ishimaru.n@tokushima-u.ac.jp
Telephone: +81-88-6337464
Fax: +81-88-6337464

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Abstract

Macrophages are key players in various immune responses. In addition to functions in innate immunity such as antigen phagocytosis and cytokine production, antigen presentation by macrophage represents a link between innate and acquired immunity. During inflammatory processes, naïve monocytes differentiate into pro-inflammatory M1 and anti-inflammatory M2 macrophages. Resident monocytes/macrophages contribute to immune response that maintains tissue-specific homeostasis. In the target organs of autoimmune diseases, macrophages have dual functions in both the induction and suppression of autoimmune responses, which are mediated by production of various cytokines and chemokines, or by interaction with other immune cells. This review focuses on selected autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and Sjögren's syndrome, to illustrate the key roles of macrophages in the cellular or molecular pathogenesis of autoimmunity. In addition, the contribution of macrophages to each autoimmune disease is compared.

Key words: Macrophage; Autoimmunity; Differentiation; Cytokines; Chemokines

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Core tip: Macrophages are well known as phagocytic cells and the source of cytokines and other immunomodulators of the innate immune system. There are many reviews of macrophage function, but not many that focus on their role in autoimmunity and autoimmune disease. This review focuses on the role of tissue resident macrophages in autoimmunity both in general and

several selected autoimmune diseases, develops a novel context for evaluation and a slightly different way of thinking of the complex interactions involved in "mistaken self-identity".

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INTRODUCTION

Autoimmunity proceeds *via* a complex interaction of immune responses by a variety of immune cells in both lymphoid and target organs^[1]. In some autoimmune diseases, T-cell-mediated autoimmune responses are involved in the onset or development of disease. Auto-reactive T cells are generated in the thymus and other peripheral lymphoid organs in an environment that includes other immune cells, stromal cells, and various epithelial cells^[2,3]. Because the activities of autoreactive T cells are regulated by interactions with regulatory T (Treg) cells, dendritic cells, macrophages, and B cells, the pathogenesis of autoimmune diseases cannot be considered simply as a T-cell-mediated immune response^[4]. The interactions of T cells with other immune cells in the pathogenesis of autoimmune disease have been described in many research reports^[5].

Macrophages differentiate from bone marrow-derived monocytes or tissue resident cells that are derived from yolk sac or fetal liver, such as histiocytes, Kupffer cells, microglia, alveolar, peritoneal, and synovial macrophages^[6,7]. In the innate immunity system, macrophages function as phagocytic cells that engulf and digest cellular debris, foreign substances, microbes, and pathogens^[8]. They also secrete cytokines and chemokines that modulate the activities of other immune cells in the inflammatory lesions^[8]. The third macrophage function in innate immune system is antigen presentation to T cells which represents a link between innate and acquired immunity as well as dendritic cell^[8]. Macrophages also contribute to the recovery of injured tissue by promoting angiogenesis or fibrosis^[9]. The functions of tissue-resident macrophages have been the topic of recent reviews.

Classically activated (M1) macrophages produce pro-inflammatory cytokines, such as interleukin (IL)-1 β , interferon (IFN)- γ , and tumor necrosis factor (TNF)- α that promote various inflammatory responses^[6,10]. Alternatively activated (M2) macrophages produce anti-inflammatory cytokines, such as IL-10 and IL-4. There are three macrophage subsets (M2a, b, and c) with characteristic stimuli or cytokine profiles^[6,10].

Although macrophages are involved in inflammatory stimuli, including autoimmunity, the lesions accompanying such responses are not induced by macrophages only. In addition, these cells also support tissue repair

and immune homeostasis restoration. Therefore, the complex pathogenesis of autoimmune diseases can be seen as reflecting macrophage dysfunction. Further, the comparison regarding the contribution of macrophages to the pathogenesis between representative autoimmune diseases would be important for understanding the cellular mechanisms of the onset or development of autoimmune diseases. We review recent studies elucidating the role of macrophages in cellular and molecular mechanisms of autoimmune disease; moreover, we discuss potential novel clinical approaches to treat autoimmune diseases by targeting macrophages.

MACROPHAGE SUBSETS

Monocytes differentiate into classically activated (M1) or alternatively activated (M2) macrophages following exposure to polarization signals such as cytokines, chemokines, hormones, bacterial products, and lipids (Figure 1A). Exposure of naïve monocytes to IFN- γ , TNF- α , or lipopolysaccharide (LPS) induces M1 development. M1 macrophages produce pro-inflammatory cytokines, including TNF- α , IL-1 β , IL-6, IL-12 and IL-23, which in turn promote development and responses of Th1 cells^[6,9]. By contrast, M2 macrophages are further classified into three subpopulations, depending on the response to various stimuli^[6,10]. Exposure of naïve monocytes to IL-4 and IL-13 promotes M2a macrophages which express arginase I and produce IL-10, TGF- β , IL-1Ra, CCL17, CCL22 and CCL24 to promote Th2 cells, eosinophils and basophils (Figure 1A)^[6-10]. M2b macrophage development is induced by LPS, immune complexes (ICs), or apoptotic cells. In turn, M2b macrophages express inducible nitric oxide synthase and produce high level of IL-10, TNF- α , IL-1 β , IL-6 and CCL1, which then promote recruitment of eosinophils and Treg cells (Figure 1A)^[6-10]. M2c macrophages are elicited by IL-10, TGF- β , or glucocorticoids and express arginase I. M2c macrophages exert an immunosuppressive function by promoting the development of Th2 cells and Treg cells (Figure 1A)^[6-10].

TISSUE MACROPHAGES

In addition to the functional macrophage subtypes, there are subpopulations of tissue resident macrophages. These include microglia in the brain, intraocular macrophage in the eye, Langerhans cells in the skin (dermal DCs), salivary macrophage in the salivary glands, alveolar macrophage in the lung, splenic macrophages, Kupffer cells in the liver, intestinal macrophages, subcapsular sinusoidal macrophages and medullary macrophage in the lymph nodes, bone marrow macrophages, and osteoclasts in bone, all of which contribute to various tissue-specific immune surveillance (Figure 1B)^[9]. For example, alveolar macrophages remove foreign antigens or allergens in the lung; Kupffer cells contribute to clearance of pathogens and toxin in the liver^[8,9]. Recent studies demonstrate that resident macrophages derives from yolk sac and fetal liver in addition to bone marrow (Figure

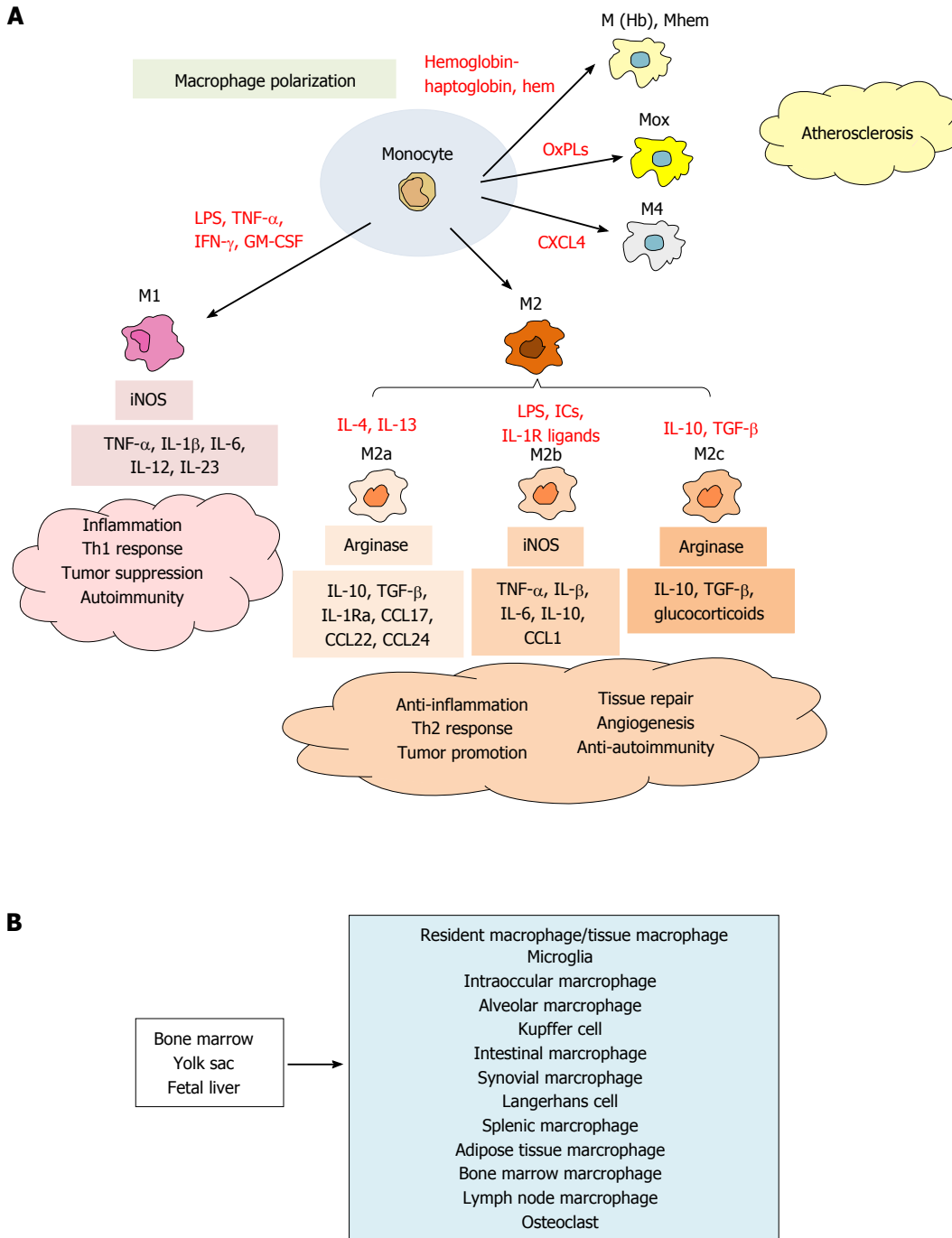


Figure 1 Macrophage differentiation and resident macrophages. A: Naïve monocytes differentiate into M1, M2 and atherosclerosis-related macrophages [M(Hb), Mox, and M4] by various stimuli. M1 macrophages enhance inflammation through producing TNF- α , IL-1 β , IL-6, IL-12 and IL-23. M2 macrophages polarize to three subsets (M2a, M2b and M2c) by cytokines or ICs to suppress inflammation and repairs tissues through producing regulatory cytokines, such as IL-10, TGF- β , IL-1R ligands and IL-6. Macrophage precursors (monocytes) are circulating, and quickly migrate into all tissues of the body, in which monocytes differentiate into mature macrophages with unique functions in each tissue; B: Resident /tissue macrophages are derived from bone marrow, yolk sac, and fetal liver to settle in various tissues. Resident macrophages contribute to homeostasis in the tissues. OxPLs: Oxidized phospholipids; ICs: Immune complexes; IFN: Interferon; TNF: Tumor necrosis factor; IL: Interleukin; MCP-1: Monocyte chemoattractant protein-1; LPS: Lipopolysaccharide; iNOS: Inducible nitric oxide synthase.

1B)^[7]. Adipose tissue macrophage (ATM) are involved in the pathogenesis of metabolic diseases such as obesity and type 2 diabetes, in which accumulation of M1 ATMs promote inflammation and insulin resistance^[11,12]. Resident macrophages are located in the all tissues, and play important roles in immune surveillance function to maintain the homeostasis.

Macrophage accumulation within the vascular wall is a hallmark of atherosclerosis. The lesional macrophages are derived from both blood monocytes and smooth muscle cells, and accumulate lipoproteins by macropinocytosis, phagocytosis, and binding to scavenger receptors, such as SR-A, SR-BI, CD36, and LOX1^[13]. The vascular subsets include M(Hb) and Mhem macrophages that are

resistant to lipid loading and are induced by hemoglobin-haptoglobin complexes and hem^[13-15]. The Mox macrophage subset is induced by exposure to oxidized phospholipids and is characterized by expression of high levels of heme oxygenase-1^[13,16,17]. In addition, M4 macrophage is induced by CXCL4, and associated with the pathogenesis of atherosclerosis (Figure 1A)^[13,16-18].

Macrophages are also a functional link between inflammation and cancer. There is strong evidence that tumor-associated macrophages (TAMs) can promote tumor progression^[19,20]. Cytotoxic killing by M1 TAMs, has an antitumor effect, but angiogenesis stimulated by vascular endothelial growth factor produced by M2 macrophages promotes tumor growth^[21,22]. A number of diverse macrophage-associated phenotypes contribute to tumorigenesis in the complex tumor microenvironment.

IMPAIRED ENGULFMENT BY MACROPHAGE AND SYSTEMIC ERYTHEMATOSUS

Impaired engulfment of dead cells by macrophage results in activation of autoimmune responses leading, severe autoimmune anemia, and chronic arthritis^[23-26]. Apoptotic cells release "find me" signals, such as lysophosphatidylcholine, to attract phagocytes and expose "eat me" signals on the cell surface that stimulate engulfment^[23,27]. One of the "eat me" signals is phosphatidylserine, which is exposed on the cell surface during apoptosis. Macrophages recognize phosphatidylserine, engulf the apoptotic cells, which are transferred to the lysosomes and degraded by lysosomal enzymes. Bridging molecules such as milk fat globule EGF factor 8 (MFG-E8) and growth arrest-specific 6 (Gas6) protein mediate binding between phosphatidylserine on the apoptotic cells, and integrin and tyrosine-kinase receptors on macrophages^[23,26]. The clearance of apoptotic cells in the body is controlled by complex molecular and cellular interaction with macrophages.

If apoptotic cells are not engulfed, then they undergo secondary necrosis, in which the plasma membrane disintegrates with release of the cellular contents, which then bind to immunoglobulins and complement proteins, and activate macrophages and B cells. In addition to Fc receptors and B cell receptors, also Toll-like receptors are able to recognize the necrotic cell components and activate macrophages and B cells. The activated macrophages secrete cytokines that stimulate B cells to produce autoantibodies able to cause pathological conditions such as systemic erythematosus (Table 1)^[23,26]. In addition, if lysosomal digestion is defective, the dead cell components accumulate in the lysosomes, leading to intracellular activation of pro-inflammatory cytokines such as IFN- β and TNF- α production by the innate immune system^[23,26]. Thus, both extracellular activation of immune responses by apoptotic cells that are not phagocytized and intracellular activation of macrophages by impaired processing of apoptotic cells contribute to the onset or development of autoimmunity.

MACROPHAGES IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a debilitating neurological disorder of the central nervous system (CNS). It is a T-cell-mediated autoimmune disease with clinical signs and symptoms characterized by weakness and progressive paralysis^[28,29]. Studies of experimental autoimmune encephalomyelitis (EAE), an animal model of MS, have demonstrated that autoreactive T cells against myelin proteins play a key role in disease development^[30,31]. Th1 and Th17 cells trigger autoreactive responses within the CNS through pro-inflammatory cytokines including IFN- γ , IL-17, IL-12, and IL-23. At later phases of MS, Th2 and Treg cells contribute to controlling inflammation.

Macrophages participate in the pathogenesis of EAE^[32,33]. Indeed, there are few infiltrating macrophages in the CNS under physiological conditions. However, during induction and exacerbations of EAE, macrophages infiltrate the meninges surrounding the CNS, the perivascular space, and the choroid plexus^[34,35]. The number of infiltrating macrophages in the CNS decreased during remissions in parallel with the decrease in lymphocyte infiltrates^[34,35]. The expression of chemokines and chemokine receptors by CNS macrophages contributes to the induction and progression of EAE^[36]. EAE studies have demonstrated that up-regulation of CCR2, CCL2, CCL3, CCL4 and CCL22 induces macrophage accumulation and effector function in the CNS^[37,38]. Moreover, CCR4, a receptor for CCL17 and CCL22, is up-regulated in macrophages present in the CNS lesions^[39]. CCR4 gene knockout mice exhibit lower macrophage infiltrates in the CNS, and exhibit milder EAE symptoms than those seen in wild type mice^[40].

Both M1 and M2 macrophages play important roles in enhancing and regulating the pathogenesis of EAE. TNF- α , IL-1 β , IL-12 and nitric oxide, expressed by activated M1 macrophages, induce inflammation and tissue damage in the CNS^[41-43]. Fewer M2 than M1 macrophages are present in the CNS during exacerbations in EAE mice. An increase in the M2 macrophage population contributes to anti-inflammatory effect associated with increased production of IL-4, IL-10, IL-13 and TGF- β ^[44]. Moreover, M2 macrophages are thought to have more regulatory function in the pathogenesis of EAE^[45]. In addition to tissue repair, the anti-inflammatory cytokines produced by M2 macrophages drive differentiation and recruitment of Th2 and Treg cells to suppress the autoimmune response in EAE^[45]. Adoptive transfer of M2 macrophages into EAE mice significantly inhibits disease development^[41,44]. Thus, macrophages play key roles in the pathogenesis of MS (Table 1).

MACROPHAGE IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune

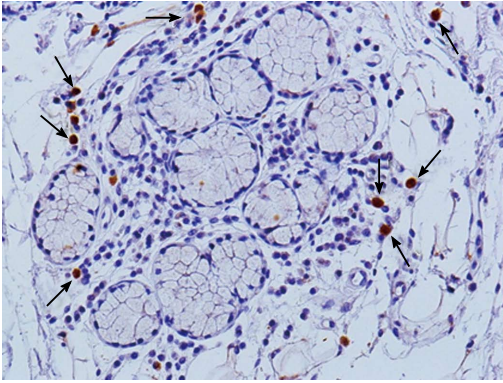


Figure 2 Macrophages in autoimmune lesions. CD68⁺ macrophages infiltrate in the salivary gland tissue from SS patients. Immunohistochemical analysis using paraffin-embedded sections from lip biopsy materials was performed by staining with anti-CD68 antibody (DAKO). Biotinylated antibody and horseradish peroxidase (HRP)-conjugated streptavidin (LSAB kit, DAKO) was used as a secondary antibody, and then CD68⁺ cells were detected by using 3,3'-Diaminobenzidine (DAB) as a substrate. Counter staining was performed with hematoxylin. Original magnification is $\times 400$. Arrows show CD68⁺ macrophages.

disorder characterized by inflammation of the synovial lining of the joint capsule. Pathological characteristics of RA lesions include immune cell infiltration, synovial cell hyperproliferation, fibrosis (pannus formation), and destruction of cartilage and bone^[46]. Various immune cells are observed in RA lesions, including CD4⁺ T cells, CD8⁺ T cells, B cells, natural killer (NK) cells, $\gamma\delta$ T cells, mast cells, dendritic cells, and macrophages^[47,48]. Monocyte/macrophage-derived cytokines, such as TNF- α , IL-1 β , IL-12, IL-6, IL-15, IL-18 and IL23, trigger and enhance the activation and recruitment of Th1 and Th17 T cells in the synovial tissues of RA patients and animal models^[49]. In addition, activated macrophages also play an important role in controlling Treg cells in the pathogenesis of RA^[49,50].

Synovial macrophages are resident cells in the synovial tissues of healthy joints^[49]. The macrophages become activated and polarized to form M1 or M2 phenotype within RA lesions. However, inflammatory synovial macrophages have not yet been classified into a phenotype. Many M1 macrophages that produce TNF- α and IL-1 β are observed in the synovial tissues of RA patients along with M2 macrophages that produce IL-10. The ratio of M1 to M2 macrophages present in synovial lesions varies in relation to disease stage. IFN- γ and TNF α promote polarization to M1 macrophages during synovial inflammation in early stage disease^[51,52]. IFN regulatory factor (IRF) 5 is thought to be a key transcription factor for M1 macrophage differentiation^[53]. IL-10, IL-4, IL-13 and ICs promote polarization to M2 macrophages and suppression of synovial inflammation at later stage^[54]. M2 macrophage differentiation is controlled by a lot of number of transcription factors, including IRF3, IRF4, and nuclear factor (NF)- κ B (Table 1)^[55-57].

Therapies targeting monocyte/macrophage have been used to treat RA. Inhibition of TNF- α produced by synovial inflammatory macrophages promotes IL-10 expression

by CD4⁺ T cells, enhances Treg cell function, promotes monocyte apoptosis via transmembrane (tm)TNF- α , and is associated with an antiosteoclast effect^[58-63]. Inhibition of IL-6 signaling enhances the frequency of Treg cell, and monocyte apoptosis^[64-69]. Abatacept [cytotoxic T-lymphocyte antigen 4-Ig (CTLA4-Ig)] inhibits both the interaction between monocytes/macrophages and T cells, and monocyte differentiation into osteoclasts^[70]. Therefore, macrophages contribute to the pathogenesis of RA directly or indirectly. Clinical use of agents that target macrophage function would likely be effective for treating RA.

MACROPHAGES IN SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a chronic autoimmune disease that targets exocrine glands, such as salivary and lacrimal glands, and also causes systemic autoimmune lesions^[71]. The mononuclear cell populations infiltrating the salivary gland tissues of SS patients include CD4⁺ T cells, CD8⁺ T cells, Treg cells, B cells, NK cells, DCs and macrophages^[72]. Among them, infiltration of CD4⁺ T cells, Treg cells, B cells, DCs and macrophages is correlated to lesion severity^[73]. SS is triggered by T-cell-mediated autoimmune responses; however, also other immune cells contribute to the onset or development of SS, including macrophages. Macrophages are observed in the autoimmune lesions of the salivary gland tissues from SS patients (Figure 2). Indeed, an elevated expression of macrophage-derived molecules, such as chitinase-3-like protein 1 and chitinase 1, is associated with increased severity of SS lesions, suggesting that macrophages are involved in the pathogenesis of SS^[74]. In addition, pro-inflammatory cytokines produced by macrophages, such as TNF- α , IL-1 β , IL-6 and IL-12, have been associated with the induction of autoimmune lesions in the target glands of MRLlpr/lpr mice, a murine model of SS^[75]. In a SS model using autoimmune regulator (*AIRE*) gene knockout (KO) mice, many macrophages in addition to CD4⁺ T cells infiltrated the corneal stroma, limbus, and lacrimal glands^[76]. Adoptive transfer of CD4⁺ T cells from *AIRE* KO mice into immunodeficient recipient mice resulted in local infiltration of macrophages in the target tissue^[76]. Moreover, *in vivo* depletion of macrophages by injection of clodronate liposome into *AIRE* KO mice attenuated dry eye symptoms^[76]. Therefore, autoreactive T cells may elicit macrophage infiltration into the target organs of macrophage-associated autoimmune lesions (Table 1).

Aromatase is an enzyme that converts androgens to estrogens. Aromatase gene knockout (*ArKO*) mice develop marked abdominal adiposity, suggesting that aromatase regulates lipid metabolism^[77,78]. *ArKO* mice also spontaneously develop an autoimmune disease in exocrine glands, such as salivary and lacrimal glands that resembles SS^[79]. We reported significantly increased expression of mRNA encoding pro-inflammatory cytokines, IL-1 β , IL-6, IFN- γ , TNF- α , and monocyte che-

Table 1 Autoimmune diseases and macrophages

Autoimmune disease	Remarks of macrophage
SLE	Impaired engulfment, IFN- β , TNF- α , B cell activation
MS	M1 (CCR4, TNF- α , IL-1 β , IL-12, NO), M2 (IL-4, IL-10, IL-13, TGF- β)
RA	M1 (TNF- α , IL-1 β , IRF5), M2 (IL-10, IL-4, IL-13, IRF3, IRF4, NF- κ B)
SS	M1 (IL-1 β , IL-6, TNF- α , MCP-1)

SLE: Systemic erythematosus; MS: Multiple sclerosis; RA: Rheumatoid arthritis; SS: Sjögren's syndrome; IFN: Interferon; TNF: Tumor necrosis factor; IL: Interleukin; IRF: IFN regulatory factor; MCP-1: Monocyte chemotactic protein-1.

motactic protein-1 (MCP-1) in white adipose tissue of ArKO mice^[80]. We also found an increased number of inflammatory M1 macrophages in white adipose tissue of ArKO mice, and significant enhancement of MCP-1 mRNA expression in the salivary gland tissue^[80]. The severity of autoimmune lesions in a murine SS model exacerbated by administration of an aromatase inhibitor, and the percentage of macrophages in the spleen of SS model mice treated with aromatase inhibitor was significantly higher than that in control mice^[80]. Collectively, the data indicates that aromatase may be involved in the pathogenesis of SS-like lesions by controlling the target organ- and adipose tissue-associated M1 macrophages.

CONCLUSION

Macrophages have dual functions in promotion and regulation of inflammation. The differentiation and distribution of macrophages influence the onset or development of systemic and organ-specific autoimmune diseases. Macrophages serve as a bridge between innate and adoptive immunity to maintain immunological homeostasis, and macrophage dysfunction or impairment leads to the induction of severe immune disorder. Clinical interventions targeting macrophages may result in discovery of novel treatments of immune disorders, including autoimmune diseases.

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Penicillamine and auto-immunity: Relationship or coincidence?

Sofia Santos, Raquel Faria

Sofia Santos, Department of Nephrology, Centro Hospitalar do Porto, 4099-001 Porto, Portugal

Raquel Faria, Department of Medicine, Centro Hospitalar do Porto, 4099-001 Porto, Portugal

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Correspondence to: Sofia Santos, MD, Department of Nephrology, Centro Hospitalar do Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal. sofia.fersantos@gmail.com
Telephone: +351-22-2077500
Fax: +351-22-2033189

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Abstract

Drug induced lupus is an established and recognised entity, and penicillamine is one of the drugs that induce it. But the uncertainty remains: Could penicillamine trigger

autoimmunity in a broad-spectrum or in a particular way?

Key words: Penicillamine; Auto-immunity; Drug induced lupus

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Core tip: Penicillamine and auto-immunity: Relationship or coincidence?

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TO THE EDITOR

Due to its metal chelation properties D-penicillamine is widely used for the treatment of some human diseases, such as Wilson's disease. However, many adverse reactions have been repeatedly reported to its use and it has been frequently described as an autoimmunity inducer, including drug-induced lupus (DI-L)^[1]. There is evidence that penicillamine binds to aldehydes on the surface of macrophages and this leads to their activation, which in some patients can lead to an autoimmune syndrome^[2]. Also, studies suggest that Th17 cells are involved in the pathogenesis of this penicillamine-induced autoimmunity^[3]. We can inquire about the mechanism of this interaction: Whether we face a drug reaction that results in a specific autoimmune-like disease; or instead this drug plays its role prompting autoimmunity in an unspecific way.

The authors present two cases that highlight this doubt.

Case 1, a 20-year-old woman was treated with

D-penicillamine for Wilson's disease for seven years. She developed complaints of symmetrical joint pain, constitutional symptoms and alopecia. The blood test revealed anemia (7.1 g/dL), leucopenia (2900/ μ L), speckled anti-nuclear antibody 1/1280, positive antihistone antibodies, anti-dsDNA and anti-Smith. It was assumed as DI-L and she stopped D-penicillamine. Nevertheless the disease progressed in the next six years with sustained arthritis, purpura, Raynaud's phenomenon and renal involvement: proteinuria 4.5 g per 24 h plus red blood cells, increasing serum creatinine, and complement consumption. The renal biopsy performed 6 years after suspension of D-penicillamine established the diagnosis class III lupus nephritis (ISN/RPS). Even though drug induced lupus erythematosus has some features in common with systemic lupus erythematosus (SLE), they are distinct entities. In this case, the clinical course led us to the diagnosis of *de novo* SLE. To our knowledge there is only one previous case report that shows a similar description^[4].

Case 2, a 39-year-old woman who at the age of fourteen had a diagnosis of Wilson's disease. After 18 years of treatment with D-penicillamine she started a polyarticular disease with a gradual onset and migratory joint involvement, specially metacarpophalangeal and proximal interphalangeal joints, as well as wrists and

ankles. The immunological study showed high positive rheumatoid factor and anti-citrullinated protein antibodies. Also in this case, in spite of the withdrawal of D-penicillamine therapy there was progression of the clinical features. To our knowledge there is no other report in clinical literature that connects seropositive rheumatoid arthritis and Wilson's disease with penicillamine-induced disease.

DI-L is an established and recognised entity, and penicillamine is one of the drugs that induce it. But the uncertainty remains: Could penicillamine trigger autoimmunity in a broad-spectrum or in a particular way?

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Holistic paradigm in carcinogenesis: Genetics, epigenetics, immunity, inflammation and oral infections

Sok-Ja Janket, Marium Qureshi, Antonio Bascones-Martinez, Jerian González-Febles, Jukka H Meurman

Sok-Ja Janket, Department of Periodontology, Boston University H. M. Goldman School of Dental Medicine, Boston, MA 02118, United States

Sok-Ja Janket, Marium Qureshi, Department of General Dentistry, Boston University H. M. Goldman School of Dental Medicine, Boston, MA 02118, United States

Antonio Bascones-Martinez, Jerian González-Febles, Department of Oral Medicine and Surgery, Complutense University, 28040 Madrid, Spain

Jukka H Meurman, Department of Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, 02160 Helsinki, Finland

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Correspondence to: Sok-Ja Janket, DMD, MPH, Department of Periodontology, Boston University H. M. Goldman School of Dental Medicine, 100 East Newton Street, Room B08A, Boston, MA 02118, United States. skjanket@bu.edu
Telephone: +1-617-4141066
Fax: +1-617-4141061

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Abstract

Recent debate among the experts of cancer research regarding the main causes of carcinogenesis encouraged us to review the etiology of cancer pathogenesis. The somatic mutation theory attributes carcinogenesis to random errors in DNA multiplication while the tissue organization field theory ascribes causation to environmental factors. We recognize complexity in cancer pathogenesis and accept the premise of both DNA multiplication errors and environmental factors in cancer development. Furthermore, it should also be noted that the combination of these factors and the relative importance of the each differ in various types of cancers. For example, in some cancers, genetics plays a prominent role while in others environment such as obesity plays a much stronger role. Additionally, the cancer mitigating factors should also be considered. The balance of cancer-enhancing and cancer-suppressing forces determines the cancer incidence. Ultimately, identifying the lifestyle factors that revise somatic mutations or epigenetic alterations will lead to a clear understanding of pathogenic mechanisms of cancer and to the optimal preventive strategies. This narrative review evaluates the published evidence on carcinogenesis pertaining to the whole organism (thus, holistic) incorporating genetics, epigenetics, immunology, inflammation and infections with emphasis on oral infections.

Key words: Genetics; Carcinogenesis; Inflammation; Epigenetics; Immunity; Infections

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Core tip: A recent debate among renowned scholars prompted us to review cancer pathogenesis in a holistic approach. One group attributed cancer to “random errors in DNA multiplication” (Tomasetti C, *Science*, 2015) while other experts credited environmental factors for cancer causation (Wu S, *Nature*, 2016). However, we put forward the concept that cancer is multifactorial and both intrinsic (DNA multiplication errors) and extrinsic (environmental) factors contribute to carcinogenesis. In this review, we examined these risk factors in some detail covering genetics, epigenetics, immunity, inflammation and infections. We acknowledge the contribution of each risk factor is different in various types of cancer. In some cancers, genetics plays a powerful role while in others, metabolism contributes a stronger impact. Therefore, a holistic understanding of carcinogenesis is truly necessary considering multi-system involvement in cancer development.

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INTRODUCTION

Approximately 1.5 million new cases of cancer are diagnosed each year^[1] and nearly 600000 persons will die from the disease^[1]. Recent debate among experts^[2,3] on carcinogenesis can be categorized into two major theories: Bad luck in DNA multiplication^[2] or environmental factors^[3]. Somatic mutation theory (SMT) is in support of the thesis that all cancers are caused by somatic mutations^[4], namely as consequences of errors in DNA replication. However, a new tissue organization field theory (TOFT) paradigm considers that carcinogenesis takes place at the tissue level, and carcinogenesis is a reversible process^[5].

The ever increasing rates of cancer in the last century can be explained by the concurrent burgeoning endocrine-metabolic, inflammatory, neurodevelopmental or neurodegenerative chronic diseases and their epigenetic influence on tissue programming. The somatic mutations can lead to changes at the cellular, genetic, and epigenetic levels that transform normal cells to a malignant mass by permitting and promoting uncontrolled cell division^[6]. The somatic mutations include: (1) substitutions of one base for another; (2) insertions or deletions of small or large segments of DNA; (3) re-arrangements, in which DNA has been broken and then rejoined to a different DNA section; (4) gene amplification which increases gene numbers from normal diploids to ploidy of several hundred; or (5) total deletion of genes^[7]. Cancer cells may also acquire totally foreign DNAs from viruses. The DNA

contributing viruses are human papilloma virus (HPV), human herpes virus 8, Epstein Barr virus, and hepatitis B virus^[7]. On the contrary, TOFT considers cancer “results of a disruption of cell communication needed to maintain normal tissue structure and function”^[8].

Additionally, epigenetics is a process where external or environmental factors silence some gene expression or enhance others and thus can increase or decrease cancer occurrence. However, epigenetic changes are correlated with gene mutation and the demarcations between genetics and epigenetics become unclear^[9,10]. Our opinion is that both genome based SMT and epigenome based TOFT are interlaced in carcinogenesis and that genetics and epigenetics converge in the end. This interpretation has been shared by several leading researchers^[10,11]. One point of note is that in some cancers the genome may have more powerful impacts while in others the epigenome may influence carcinogenesis more strongly.

Lifestyle and biologic factors can also modify somatic mutations. These factors include ageing, smoking, alcohol intake, exposures to ultraviolet light or chemicals such as pesticides, obesity and infections^[12]. Thus, the progressive accumulation of minor mutations in the normal aging process also increases the risk of cancer. For this reason, ageing is the biggest cancer risk that affects everyone. Because many cancers occur from or in the vicinity of inflammation sites, inflammation was hypothesized to coordinate carcinogenesis^[13]. However, this concept was largely invalidated by a disappointing failure of the trials to suppress inflammation for the purpose of reducing cancer incidence^[14].

Recent theory suggests that cancer initiation is driven by a disruption in the quorum sensing mechanism, either by genetic mutations, or by the environment^[8]. Quorum sensing (QS) can be interpreted as a communication and response mechanism in a community of cells that maintains the integrity of the community. When QS disruption causes dysfunction in sensing, it weakens the tissue defense and the community is vulnerable to cancer development^[8]. The majority of QS disruption does not cause cancer because the immune system quickly removes aberrant and undesirable molecules before they progress to malignancy. These findings confirm that immune dysfunction can be an integral part of oncogenesis^[15]. Thus, holistic understanding of carcinogenesis is the key to the prevention of cancer. The underlying cancer biology should include: (1) genome instability; (2) evading immune destruction; (3) infection/inflammation; and (4) energy metabolism. Clearly, cancer is a multifactorial disease as we illustrated in Figure 1 but the relative importance among these factors in cancer pathogenesis is yet to be elucidated. If the number of publications may reflect the relative importance, it will be of interest to tabulate the publication metric which is presented in Table 1. We will discuss these multisystem involvements in carcinogenesis individually in some detail.

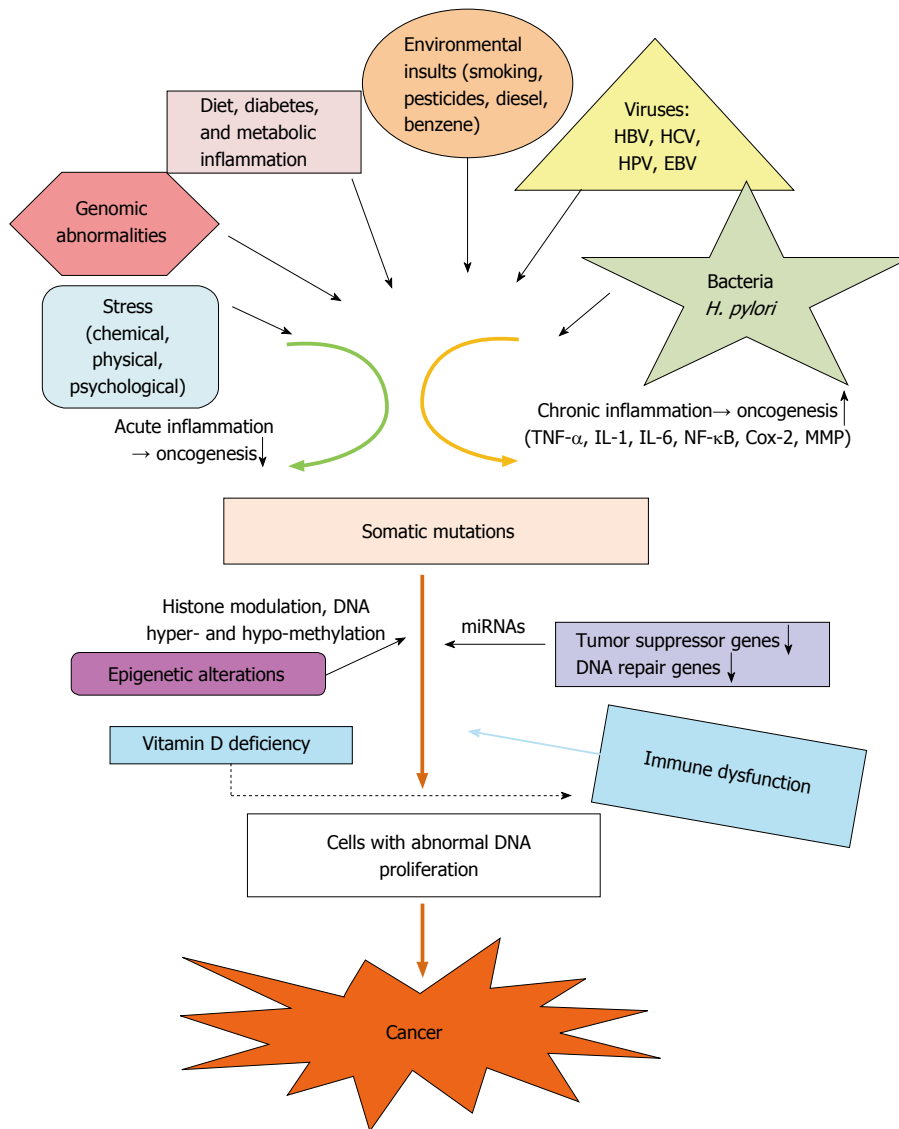


Figure 1 Postulated mechanism of carcinogenesis. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HPV: Human papilloma virus; EBV: Epstein Barr virus; TNF: Tumor necrosis factor; IL: Interleukin; NF-κB: Nuclear factor-κB; MMP: Matrix metalloproteinase; *H. pylori*: *Helicobacter pylori*; miRNAs: MicroRNAs; Cox: Cyclooxygenase.

IMMUNOLOGY OF ONCOGENESIS

According to the currently accepted paradigm, the immune system has the ability to regulate cancer initiation and progression while cancer cells have the ability to evade immune actions by expressing molecules that will incapacitate immune intervention. Thus, understanding and manipulating this dynamic relationship became the focus of current cancer therapies.

The innate immune system plays an important role in cancer development. When immune surveillance is normal, the innate immune system quickly triages the stimuli by correctly identifying whether they are harmless, part of the self, or harmful. Typically, appropriate actions will follow, namely, tolerance if harmless and part of self, or destruction if harmful^[16,17]. Unfortunately, cancer cells can manipulate immune cells such as macrophages and T-cells to their advantage

and deceive them to tolerate aberrant cancer cells by creating immune privileged micro-environments. This is clearly demonstrated by normally host defensive and cancer suppressing macrophages can subvert normally M1 type actions and shift to M2 type activities^[18]. This alteration in macrophages' role results in cancer promoting tumor-associated macrophages (TAMs) which express much lower levels of cytotoxic cytokines than its M1 counterpart^[19]. M1 pathways are pro-inflammatory, bactericidal, and tumoricidal and thus tumor suppressive. However, M2 pathway promotes anti-inflammatory activities expressing cytokines such as IL-10, transforming growth factor-β and IL-4. Moreover, M2 macrophages are poor antigen presenters and diminish T-cell functions. Additionally, TAMs support wound healing and tissue repair that are favorable to tumorigenesis. These facts strongly indicate that macrophages can be either pro- or anti-inflammatory depending on the environment they

Table 1 Cancer pathogenesis literature metrics stratified by risk factor categories

Risk factor category	No. of articles published
Genetics	379694
Infections	85420
Immunity	52889
Epigenetics	43505
Inflammation	37930
Oral infections and periodontitis	5612

Not all publications report causal relationship.

are situated^[20]. TAMs in cancer microenvironment are involved in DNA damage, oncogenic transformation in the pre-tumor stage and promote cell proliferation and survival of tumor cells in established malignancy^[21]. TAMs within the cancer microenvironment play crucial roles in oncogenesis, metastasis and manipulation of the adaptive immune system by manipulating effective T-cells^[22].

The two important molecules that suppress T-cell function are cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed cell death protein-1 (PD-1)^[23]. The cancer cells express PD-L1, a PD-1 ligand, and when PD-L1 binds PD-1, this complex becomes the inhibitors of T and B cell responses. PD-L1 and PD-L2 are upregulated in head and neck squamous cell carcinoma (HNSCC) cells cultured with an oral pathogen, *Porphyromonas gingivalis* (*P. gingivalis*) *in vitro*. However, co-culturing with *Streptococcus salivarius* K12 did not upregulate PD-L1 or PD-L2^[24].

Through these mechanisms the immune system can be forced to tolerate even non-self-antigens, and cancers occur when coexisting epigenetic mutations allow neo-antigens to proliferate. These facts underscore the intimate relationship of the immune system and cancer pathogenesis. Better understanding of the immune system and tumor cells relationship has introduced several novel cancer therapies utilizing immune checkpoint blockades and encouraging the immune system to target the specific cancer cells while leaving other cells and tissues intact^[25]. These are the cutting edge bases for the personalized immunotherapy in cancer treatment.

Immunoediting, the basis for individualized cancer therapy

Immunoediting can be defined as “the interactions between the innate and adaptive immune system and cancer cells to restructure the course of cancer progression”. Immunoediting can be host-protective (and thus suppressing cancer) or tumor-promoting by establishing a favorable tumor microenvironment that facilitates tumor growth.

The “3 Es” in immunoediting

Elimination: Elimination occurs when the immune system is competent and strong enough to produce

powerful immune reactions. Under the attack of a strong immune system, tumor cells express stress-induced molecules that are recognized by CD8+ effector cells and natural killer (NK) cells. Activated effector cells can express IFN- γ that inhibits tumor cell proliferation, and angiogenesis and CD8+ T cells can induce tumor cell apoptosis. Thus, tumor cells are completely eliminated^[26].

Equilibrium: In the second scenario, immune destruction of cancer cells is not complete but tumor cells do not proliferate and stay dormant. Cancer eliminating cytokines such as IL-12 and IFN- γ are balanced by the action of cancer-tolerant IL-10 and IL-23. Other cytokines such as IL-4, IL-17A, IFN- α/β and NK cells stay out of this battle.

Escape: In the third scenario, tumor cells escape the immune assaults and proliferate. Tumor cells avoid immune recognition *via* weaker tumor antigens, or loss of MHC class I as well as the lack of co-stimulatory molecules. In this condition, the cancer cells increase resistance to apoptosis through several mechanisms: (1) by expressing STAT-3 or anti-apoptotic molecule Bcl2; (2) by creating immunosuppressive microenvironments by expressing vascular endothelial growth factor, transforming growth factor beta; or (3) by producing immunoregulatory molecules such as PD-1/PD-L1 complexes that suppress T-cell actions^[26].

Individualized immunotherapies

Currently popular cancer treatment strategies include “targeted immunotherapies”^[25]. Fundamental principles of this strategy are awakening the checkpoints designed to suppress an over-zealous immune system to prevent autoimmunity. These check points involve molecules such as CTLA-4 and PD-1. By blocking these T-cell inhibitor molecules, T-cells can be energized and encouraged to attack tumor cells^[27]. The FDA approved several targeted cancer therapies, namely ipilimumab, a monoclonal antibody against CTLA-4 in 2011, PD-1 antibodies pembrolizumab and nivolumab in 2014, and PD-L1 inhibitor atezolizumab in 2016.

Basic understanding on immunological and inflammatory findings in relation to carcinogenesis is presented in Table 2.

GENETICS IN ONCOGENESIS

Epigenetics and cancer

Epigenetics is defined as genetic control by factors other than an individual's DNA sequence *via* silencing certain genes while promoting others. These processes involve regulating transcription factors, access to chromatin, chromatin-chromatin interactions, expressing micro-RNAs (miRNA) or long non-coding RNAs (lncRNA) that control the expression of mRNA^[28]. One may be tempted to say that epigenetics controls gene expression. However, epigenetic manifestations such

Table 2 Summary of inflammation and cancer relationship

Basic observations	Interpretation
Chronic inflammation increases cancer risk	Causality is not proven ^[47]
AIs decrease cancer	Inflammation from psoriasis actually reduces cancer risk AIs are proven to decrease cancer risk as shown in Coley's toxin ^[95] AIs may mobilize strong immune responses and create cancer resisting environment ^[94,95]
Metabolic inflammation may be an important risk factor	Causality is quite possible, <i>via</i> IGF, VEGF
Various type of immune, inflammatory cells are present in cancer loci	They can be innocent bystanders
Immune cells affect malignant cells through cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species	This fact proves that there is an interaction between immune cells and cancer cells but causal relationship is yet to be established
Inflammation is present from tumor initiation to metastasis	It does not mean inflammation causes cancer. Inflammation may be a part of disease processes in cancer
NF-κB signaling pathway can be two-way street: NF-κB from immune system can suppress cancer progress; also NF-κB from cancer cells to resist immune action	NF-κB is universal biologic transcription factor and difficult to prove its involvement as a causal factor in carcinogenesis
Certain immune/inflammatory actions are dispensable in some stages and indispensable in others	

AIs: Acute infections; IGF: Insulin-like growth factor; VEGF: Vascular endothelial growth factor.

as histone modification are often strongly correlated with patterns of inherited gene expression^[9] and many gene mutations control the epigenome^[10], thus, the demarcation between genetics and epigenetics is not clear. Consequently, some researchers regard that genetics and epigenetics are two sides of the same construct and should be combined^[10]. During the process of tumor initiation and progression, the cancer epigenome is remodeled *via* global hypomethylation, increased promoter methylation at CpG islands, global down-regulation of miRNAs, lncRNAs or interactions between them and alterations in the nucleosome. The imbalance between transcriptionally permissive and repressive chromatin modifications may alter gene expression and lead to cancer^[29].

The role of oral infections in oncogenesis remains ill-defined, however. It has been hypothesized that chronic inflammation such as in periodontitis has the potential to provoke epigenetic modifications^[30] leading to DNA and histone methylations that contribute to oncogenesis. However, any bone modulation will involve these histone modifications^[28], and periodontitis, which involves bone loss, may also cause histone modulation.

Histone modulation, DNA methylation and other gene alterations

DNA methylations occurring in the CpG islands where the clusters of CpG sequences appear in the promoter regions, prevent transcriptional initiation and silence the genes^[31]. Differential methylation patterns associated with apoptosis, lipopolysaccharides (LPS) signaling, cell adhesion and oncogenesis have been observed in untreated periodontitis tissues^[30]. DNA methylation is necessary for normal cell development and is essential in tissue specific gene transcription^[32]. Histone acetylation and down regulation of DNA methyltransferase 1 (DNMT1) was reported in oral dysbiosis^[33]. This study has proven that epigenetic changes may indeed be associated with oral dysbiosis.

DNMT1 is overexpressed in many cancers^[34]. Thus, reduced DNMT1 in oral dysbiosis is not in agreement with the trend fostering oncogenesis. Parenthetically, reduced DNMT1 is in the same direction of cancer inhibition drugs such as 5-azacitidine or decitabine. Additionally, other lifestyle factors such as protein-restricted diets and weight loss also reduced DNMT1 expression^[35]. These observations suggest that DNA methylation may be confounded by metabolic inflammation^[17].

In general, histone acetylation is associated with enhanced transcription of genes^[31], nucleosome assembly, chromatin folding, DNA damage repair, and replication^[36]. However, the location and the gene involved will determine supporting or suppressing oncogenesis^[36]. Histone acetylation has been shown to regulate tumor suppressor gene p53, or proto-oncogene c-Myb. These indicate that histone acetylation can up- or down-regulate oncogenesis^[37]. Selected cancers in relation to epigenetic alterations are listed in supplemental Table 1.

Role of miRNAs

miRNAs are a group of small, noncoding RNAs that play key roles in epigenetic regulation by controlling the translation and stability of mRNAs. They are crucial in developmental processes, apoptosis, and cell proliferation^[38]. However, this regulation depends on the activities of other co-factors, DNA methylation and/or histone acetylation. The other co-factors include RNA-binding protein, CREB-binding protein or E1A binding protein p300 and Cyclic AMP response element-binding protein. This regulation indirectly inhibits or promotes mRNA expression. Notably, the role of miRNAs in oncogenesis varies depending on the mRNA they regulate and thus can be promoters or suppressors of oncogenesis^[39]. However, in general, most miRNAs are under-expressed in cancer compared to normal tissues.

Role of lncRNAs

lncRNAs modulate cell proliferation, senescence, migration and apoptosis. They also interact with DNA, RNA and other proteins, and regulate gene expression, and other miRNA activities. The transcribed-ultraconserved regions are a segment of DNA and considered as a novel class of non-coding RNAs. UCRs are conserved, *i.e.*, unchanged between the species. Therefore, alteration in this area is unlikely to occur due to chance, and differential expressions have been observed in several cancers^[40].

Oncogenes and proto-oncogenes

Oncogenes are genes that have the potential to cause cancer and are often mutated or expressed at a high level in cancer. Proto-oncogenes are normal genes that can become oncogenes when other co-stimulating factors are present. These proto-oncogenes include *Ras*, *Wnt*, *Myc*, *ERK*, and *Trk*.

Ras proteins, also called small GTPase are a group of ubiquitously expressed proteins in all cell lines. Their roles are in cellular signal transduction, energy regulation, and scavenging energy sources. More than 30% of all human cancers - including 95% of pancreatic cancers and 45% of colorectal cancers - are driven by mutations of the *Ras* family of genes^[12]. Activated Ras proteins are master activators of other proteins ultimately leading to cell growth, differentiation and survival. Therefore, mutation in the *Ras* gene can contribute to carcinogenesis. The most prevalent *Kras* among 3 common human proto-oncogenes was associated with pancreatic cancer. *Kras* was also strongly associated with nicotine^[41], and with the receptor of advanced glycation end products^[42]. These facts suggest that smoking and glucose metabolism may be risk factors for pancreatic cancer *via* the *Kras* pathway.

Mutations in *Wnt* genes lead to a variety of diseases including breast and prostate cancers, glioblastoma, type II diabetes, and others^[43]. *Wnt* commonly co-exists with embryonic processes and cell fate specification, and cell proliferation. The canonical *Wnt* pathway leads to regulation of gene transcription, while the non-canonical pathway regulates the cytoskeleton. Thus, it is plausible why the non-canonical pathway is associated with periodontitis where bone remodeling is involved^[44]. However, nicotine also impact on *Wnt* signaling and potential confounding by smoking is possible^[45].

Myc is a regulator gene that codes for a transcription factor and plays a role in cell cycle progression, apoptosis and cellular transformation. *Myc* regulates many genes that lead to variety of cancers including carcinoma of the cervix, colon, breast, lung and stomach.

ERKs are extracellular-signal-regulated kinases, such as classical mitogen-activated protein (MAP) kinases. MAP kinases are widely expressed in the regulation of cell divisions and post-mitotic functions

in differentiated cells. Disruption of the *ERK* pathway is common in cancers. The role of microRNAs in carcinogenesis is summarized in supplemental Table 2.

INFLAMMATION IN ONCOGENESIS

Rudolf Virchow in the 19th century hypothesized that chronic inflammation might increase tissue proliferation. Chronic inflammatory states have many features in common with cancer: Inhibition of apoptosis (partly due to inactivation of p53); induction of angiogenesis; and the activation of humoral immune response^[46]. However, other metabolic conditions also express insulin-like growth factors (IGFs) and cyclo-oxygenase (Cox)-2, both of which inhibit apoptosis^[46]. IGFs are closely related to metabolic inflammation and diabetes, and elevated IGF levels were associated with breast, prostate, colorectal, and lung cancer^[46]. Therefore, Virchow's theorem that chronic inflammation (implicitly from infections) causes malignant transformation is yet to be proven. Rather, inflammation can be the result of cancer biology or can be paralleling phenomena without causal link to cancer pathogenesis. The reason is because inflammation can be either tumor suppressive or tumor promoting^[47].

The vast majority of somatic mutations involve some form of chronic inflammation. Up to 20% of cancers were linked with chronic infections, 30% may be traced to smoking tobacco or other inhalants such as asbestos or silica and 35% can be attributable to dietary factors^[48]. Subclinical and often undetectable metabolic inflammation from obesity can be a strong risk factor for liver cancer^[49]. Another type of chronic inflammation that precedes tumor development is caused by immune dysregulation and autoimmunity. The example of this is inflammatory bowel disease, which greatly increases the risk of colorectal cancer.

Universal inflammatory marker NF- κ B has been implicated in oncogenesis and also featured in oral dysbiosis^[33]. However, NF- κ B is ubiquitously expressed and controls numerous physiological processes including cell development, differentiation, immunity, metabolism and cancer. Thus, multiple confounding is possible in NF- κ B expression. The fact that type 2 diabetes patients exhibited prominent NF- κ B binding after LPS challenge compared with normoglycemic controls suggests that NF- κ B expression may be due to metabolic inflammation rather than LPS challenge^[50].

METABOLIC INFLAMMATION AND CANCER

Metabolism controls carcinogens *via* substrate availability, energy for proliferation, and cell survival. Among the multiple risk factors for oncogenesis, dysregulated metabolism is the most common and recognizable features of cancer^[51]. However, its causal relationship to carcinogenesis is incompletely defined. Recent research

revealed that a high fat diet induced intestinal dysbiosis and promoted intestinal oncogenesis in *K-rasG12D^{Int}* mice^[52]. Even more significant was the fact that cancer occurred without obesity or mucosal inflammation^[52]. From the research point of view, this study proves that adjusting obesity is not sufficient to control for metabolic inflammation.

Interestingly, butyrate supplementation prevented carcinogenesis in *K-rasG12D^{Int}*^[52] as well as *Apc^{min/+}* mice models^[53], while detrimental in *Apc^{min/+} Msh2^{-/-}* mice^[54]. This suggests that dietary changes under certain genetic conditions can either prevent or promote oncogenesis. However, they did not observe the oral bacterium *Fusobacterium nucleatum* in the intestinal cancer region^[54].

In the 1920s, Otto Warburg observed that tumor cells consumed a large amount of glucose, much more than normal cells, and converted most of it to lactic acid leading to the "Warburg effect". The Warburg effect is defined as "aerobic glycolysis" which cancer cells utilize fermentation in the presence of oxygen to rapidly convert nutrients into biomass. Highly proliferative cells need glucose to be diverted to the pentose phosphate shunt and the serine/glycine pathway to produce nucleotides, excess lipid to create new cell membranes, and amino acids for the creation of new biomass^[55].

Although reactive oxygen species (ROS) were implicated in infectious inflammation, glucose metabolism also generates ROS^[56]. This observation is in agreement with our report that infectious and metabolic inflammation are in a confounding relationship^[17].

INFECTIONS AND CANCER

Although some bacterial infections such as *Helicobacter pylori* (*H. pylori*) infections are potential causal factors for cancers, oral infections as causative factors for cancer have not been determined. To be a causal factor, oral infections must occur before the cancer manifestation. Unfortunately, most published studies in this topic were cross-sectional studies^[57] which cannot be inferred as causal association. As our knowledge on oncogenesis has expanded in recent years, new risk factors such as metabolic inflammation, *p53* mutation which involved 60% of colorectal cancers^[58] and this gene affects in early stage of adenoma to cancer conversion suggesting a causal role^[59]. Moreover, adenomatous polyposis coli (*APC*) gene mutations that involved some 83% of sporadic colorectal cancer^[60] become critical in establishing causal factors^[60,61]. Thus, we have reviewed evidence from longitudinal studies published within the past 5 years.

Longitudinal human studies on oral infections and cancer

Among the very few longitudinal studies, a population-based longitudinal study reported that serum *P.*

gingivalis antibody increased the risk of orodigestive cancer mortality^[62]. This study adjusted confounding minimally without controlling for alcohol consumption and the risk from *APC* gene mutation. Cancer risk factors are site specific, and combining oral, stomach, and intestinal cancers is problematic.

The second study linked the antibodies to several oral pathogens to pancreatic cancer^[63]. Interestingly, the authors observed that the antibodies to the commensals were associated with lower risk of pancreatic cancer. This suggests that dysbiosis may be a more appropriate risk marker than the role of a few pathogens. Dysbiosis on the other hand, can be a marker for abnormal immunity which predisposes to cancer development^[64]. Although this study adjusted for confounders reasonably well, still *APC* or *Kras* gene mutations that are highly important to pancreatic cancer were not considered. Pancreatic cancer is a basically metabolic dysfunction based disease and *Kras* gene mutations are involved in 95% of pancreatic cancers^[12].

A longitudinal study that assessed periodontal treatment by insurance claims was associated with lower risk of subsequent cancers but this study did not adjust for smoking, alcohol consumption or genetics^[65]. Another insurance claims study examined the relationship of periodontitis diagnosis to pancreatic cancer incidence in 12 years of follow-up. The researchers observed a significant increase in pancreatic cancer risk among age 65 or older persons diagnosed with periodontitis at baseline^[64]. This study is the largest by far and controlled for confounding well although some proxies were used. A more positive aspect of this study is that other infections such as viral hepatitis, and pancreatitis were adjusted. However, genetic mutations were not adjusted. Notably, *Kras* mutations were found in 71%-95% of pancreatic cancers along with the *APC* mutation^[66], and thus it is absolutely required to adjust these gene mutations in pancreatic cancer.

Recently, periodontitis was implicated as a causal factor for non-Hodgkin's lymphoma (NHL)^[67]. However, the low immunity resulting from the outcome may incite periodontitis. Thus, it is highly likely that periodontitis may be the reflection of low immunity resulting from lymphoma itself rather than a causal factor for it as we have stipulated in our letter to the editor of the *International Journal of Cancer*^[68]. Immunosuppression in NHL is biologically plausible because in non-Hodgkin's lymphoma, the circulatory system is crowded with immature lymphocytes which cannot generate strong immune responses when needed. Oral manifestations of leukemia are well-known with references dating back to 1930s and 40s^[69,70]. Thus, reverse causation (periodontitis being the result of lymphoma) is possible due to long symptom-free latency^[71]. This study did not adjust for the chemical exposure, a strong risk factor for lymphomas^[72-75]. These longitudinal studies evaluating oral infections and oncogenesis are

Table 3 Longitudinal studies on the association of oral infections with cancer

	Design/sample size/f-u	Predictor	Outcome	Methods	Results	Comments
Ahn <i>et al</i> ^[62] , 2012	Prospective follow-up study: (n = 105) Approximately 12 yr f-u	Serum <i>P. gingivalis</i> antibody and periodontitis status	ODC mortality	Cox proportional hazards regression analysis Controlled age, sex, smoking status, education, race/ethnicity and BMI	Periodontitis increase CRC risk (RR = 3.58, 95%CI: 1.15-11.16) Greater serum <i>P. gingivalis</i> IgG → non-significant increase in risk for ODC mortality	No adjustment of alcohol consumption and genetics Cox regression n = event number May be underpowered
Michaud ^[63] , 2013	Nested case-control study: n = 405 cases and 416 matched controls Approximately 10 yr f-u	Plasma antibodies to 25 oral bacteria	Pancreatic cancer	Conditional logistic regression: Matched on centre, sex, follow-up time, age collection, date and time of blood collection, fasting status and use of exogenous hormones among women Additional adjustment of smoking and BMI	High antibody level to <i>P. gingivalis</i> double the risk (non-significant) → OR = 2.11 (0.97-4.59), <i>P</i> > 0.05 High antibody levels to commensals → 45% lower cancer risk (significant): OR = 0.55, 95%CI: 0.36-0.83, <i>P</i> < 0.05	No adjustment of genetics No adjustment of metabolic oncogenes, i.e., <i>k-ras</i>
Hwang <i>et al</i> ^[65] , 2014	Age, sex matched case-control (1:2), n = 116706 Approximately 13 yr f-u	Periodontal treatment by insurance claims	Death, withdrawal from the NHI system, or any cancer diagnosis	Cox proportional hazards regression Age, sex, occupation, T2D hypertension, hyperlipidemia	HR = 0.72, 95%CI: 0.68-0.76, <i>P</i> < 0.05	No adjustment of smoking, alcohol consumption or genetics
Chang <i>et al</i> ^[64] , 2016	Prospective cohort study, n = 214890 Approximately 12 yr f-u	PD diagnosis by insurance claims	Censored or diagnosed with pancreatic cancer	Cox proportional hazards regression Adjusted for age, sex, diabetes, hypelipidemia, allergies, viral hepatitis, peptic ulcer, pancreatitis, COPD, and alcohol-related conditions	HR = 1.55 (1.02-2.33), <i>P</i> = 0.04 in the whole cohort Age ≥ 65 (HR = 2.17, 95%CI: 1.03-5.47) Age < 65 yr (HR = 0.83, 95%CI: 0.52-1.34) Men (HR = 1.72, 95%CI: 1.01-2.93; women HR = 1.33, 95%CI: 0.69-2.55)	Proxies for smoking and alcohol consumption adjusted Viral hepatitis, gastric ulcer and pancreatitis adjustment is positive Genetics was not adjusted
Bertrand <i>et al</i> ^[67] , 2016	Prospective cohort, 26 yr f-u, n = 51529	History of periodontitis assessed by questionnaire	Non-Hodgkin's lymphoma including CLL; SLL; diffuse large B-cell lymphomas; follicular lymphomas	Lymphoma in general has strong correlation to hereditary immune suppression and chemical usage, i.e., pesticides → lymphoma is prevalent in agricultural workers	Overall NHL HR = 1.30 (95%CI: 1.11-1.51) CLL/SLL HR = 1.41 (95%CI: 1.08-1.84)	Lymphoma → lower immunity → periodontitis may be a marker for suppressed immunity Chemical exposure was not controlled Reverse causation is possible due to long asymptomatic latency

CLL: Chronic lymphocytic leukemia; SLL: Small lymphocytic lymphomas; ODC: Orodigestive cancer; f-u: Follow-up; COPD: Chronic obstructive pulmonary disease; CRC: Colorectal cancer; PD: Periodontitis.

summarized in Table 3.

Animal studies on oral infections and cancer

In an elaborate murine study, 4-nitroquinoline-1-oxide induced oral squamous cell carcinoma (OSCC) and when *F. nucleatum* and *P. gingivalis* were co-cultured with cancer cells, OSCC progressed much more rapidly. These oral pathogens were not the initiating factor but rather enhancers of cancer progression^[76].

A similar experiment was conducted utilizing multiple intestinal neoplasia gene positive (APC^{min/+}) mice and also observed the enrichment of *Fuso-*

bacterium spp^[77]. Here “min” designates “multiple intestinal neoplasia” gene. Another study observed strong presence of *F. nucleatum* in colorectal cancer (CRC)^[78]. *F. nucleatum* was reported to activate the β-catenin/adhesin pathway and invades intercellular space *via* FadA adhesin^[78]. However, the initiation of CRC may still be due to genetic susceptibility as the expert speculates that *APC* gene mutation is an initiating event and the presence of *F. nucleatum* may be a consequence^[79]. Therefore, we concur with the statements that if genetic damage is the “match that lights the fire”, infection may be the “fuel that feeds the

flames^[80].

Additionally, CRCs are driven by *Kras* pathway which is highly dependent on glucose metabolism, obesity, and lipid metabolism. Also, other epigenetic changes such as site specific DNA hypermethylation, loss of p53, Cox-2, mutation of *Kras* and *Braf*, all transform benign colon adenoma to malignant adenocarcinoma^[81].

E-cadherins interact with β -catenin and maintain epithelial integrity. They not only act as physical barrier of invasion of pathogens but also provide Wnt-signaling pathway^[82]. Loss of e-cadherins preceded the appearance of malignancy^[83].

E-cadherins compete with APC, a tumor suppressor gene, thus become a risk factor for CRC, for β -catenin binding^[84]. The close relationship of β -catenin and APC should be noted. Thus, potential confounding is conceivable through the ubiquitous Wnt/ β -catenin signaling pathway. Moreover, cellular permeability was a risk factor for colon cancer and intestinal permeability is increased in metabolic inflammation^[17]. Thus, it is uncertain whether *F. nucleatum* is a cause for oncogenesis or an opportunistic commensal microorganism that exploits diminished adhesion and translocates to the cancer site.

Oral virus infections and cancer

All human herpes viruses can evade immune surveillance and suppress the immune system and thus, once infected, they can stay dormant and be re-activated under certain conditions. Among these, EBV and KSHV are recognized as oncogenic viruses^[85]. EBV was persistently present in oral mucosa and detected in OSCC, and also in nasopharyngeal cancer. However, detection does not confirm their causal role in oncogenesis.

Oral HPV has been implicated in uterine and head and neck cancers^[86]. HPVs promote malignancy by mutating the tumor suppressor gene p53 by their oncoproteins E6 or E7^[87]. However, HPV infections are often co-infected with a more sinister Epstein-Barr virus. Also, smoking and alcohol consumption coexist with HPV and this fact suggests that the role of HPV can be as an opportunistic bystander. Several researchers claimed that HPV might be a causal factor for head and neck cancers but we did not find any longitudinal data to support the causal relationship. Most references in this area were cross-sectional studies in case-control format with very short follow-up. A prominent expert in this field quoted that the World Health Organization (WHO) determined that HPV infection was the cause for HNSCC^[88]. When we verified the evidence in the WHO website, we found only several case series as evidence for the causal association of HPV and cancer. Case-series or even case-control study results are hardly sufficient evidence for causality establishment in the evidence-based medicine^[89]. At the present, the existing

evidence is not solid enough to establish a causal role of HPV infection in oral carcinogenesis. In a longitudinal study, Gillison *et al.*^[88] reported that "the seropositivity to HPV is not a marker for infection nor do HPV16 L1 antibodies protect from infection"^[90]. Interestingly, the current HPV vaccination uses HPV16 L1 to induce antibodies^[91]. Thus, the utility of this vaccine for HPV prevention is of questionable value. Only 1% of population have oral HPV type 16 that is found in oropharyngeal cancers^[92] and this can be interpreted that 99% of HPV infections are not associated with oral malignancy. Considering the totality of evidence, we concur with the expert not associated with this particular group^[91] and also with the view of the Centers for Disease Controls and prevention in that "It is unclear if having HPV alone is sufficient to cause oropharyngeal cancers, or if other factors (such as smoking or chewing tobacco) interact with HPV to cause these cancers". <http://www.cdc.gov/std/hpv/stdfact-hpvandoropharyngealcancer.htm>.

Many experts consider that the presence of oral bacteria in cancer tissues may be the consequence of the cancer microenvironment^[79] or marker for immune dysfunction which predisposes to cancer^[64]. Some microorganisms can translocate to the lesion where cancer microenvironments engender low immunity. Especially in non-Hodgkin's lymphomas that accompany generalized low immunity due to dysfunctional lymphocytes, periodontitis may be one of the manifestations of this low immunity^[67]. Some measure of host immunity should be adjusted to reach an unbiased assessment of the relationship between oral infections and carcinogenesis. More importantly, a prediction model to evaluate the relative importance of each factor to carcinogenesis is necessary to prevent siphoning limited resources to minor risk factors.

CONCLUSION

Genetics, immunity epigenetics and inflammation may play major roles in carcinogenesis. Most notably, inflammation from endogenous sources (metabolic inflammation) is a strong contributor, while inflammation from exogenous infection may play a minor role in cancer development^[17] with few exceptions such as *H. pylori* in gastric cancers.

Although we found some indications that oral infection may contribute to carcinogenesis, we are unable to determine whether there is unequivocal evidence that oral infections are independent cause for carcinogenesis. The reason is that the key initiating factors, the gene mutations^[4] were not controlled in any studies. Ignoring APC mutation in colorectal cancers or *Ras* protein's role in pancreatic cancer will result in biased conclusion. Additionally, periodontitis is an inflammatory/immune-related disease and systemic immunity affects its manifestation.

It is, therefore, possible that low host immunity

may connect cancer and periodontitis but the causal contribution of oral infection to carcinogenesis is questionable. However, there is limited evidence that oral infections may promote the progression of cancer^[76,77]. Further studies are needed to examine the role of oral infections in carcinogenesis *via* the holistic approach considering the multisystem in the whole human body.

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Role of interleukin-1-family cytokines on effector CD4 T cell differentiation

Thaiz Rivera Vargas, François Martin, Lionel Apetoh

Thaiz Rivera Vargas, François Martin, Lionel Apetoh, INSERM, U1231, 21000 Dijon, France

Thaiz Rivera Vargas, François Martin, Lionel Apetoh, Faculté de Médecine, Université de Bourgogne, 21000 Dijon, France

Lionel Apetoh, Centre Georges François Leclerc, 21000 Dijon, France

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Correspondence to: Dr. Lionel Apetoh, INSERM, U1231, 7 Bd Jeanne d'Arc, 21000 Dijon, France. lionel.apetoh@inserm.fr
Telephone: +33-3-80393371
Fax: +33-3-80393434

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Abstract

The ability of CD4 T cells to differentiate into various effector or regulatory T cell subsets explains the successful adaptation of immune responses to different types of infectious pathogens. Immune responses in the context of cancer are also shaped by CD4 T cells, which can directly affect cancer prognosis in patients. While the proinflammatory mediator interleukin (IL)-1 β was initially shown to enhance Th2 cell responses, recent findings support a predominant role of two other members of the IL-1 family, IL-18 and IL-33, on the production of Th1 and Th2-derived cytokines. In addition, IL-1 β was found to profoundly affect the biology of two recently identified CD4 T cell subsets, Th17 and Th9 cells. IL-1 β is critical for Th17 cell differentiation and it enhances the production of IL-9 and IL-21 by Th9 cells, thus increasing their anticancer properties. We will here review the mechanisms accounting for the ability of IL-1 cytokines to affect the differentiation of CD4 effector T cells with a focus on Th17 and Th9 cells. The physiopathological relevance of IL-1-driven effects on CD4 T cells will also be discussed.

Key words: Inflammation; Innate immunity; Adaptive immunity; CD4; Th17; Th9; Interleukin-1; Inflammatory diseases; Cancer

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Core tip: While the proinflammatory activities of interleukin (IL)-1 have been studied since the late 1970s,

the ability of IL-1 family members to affect CD4 T cell differentiation, one key process in shaping adaptive immune responses, has only been characterized recently. Specifically, IL-1 family members can endow CD4 T cells with proinflammatory abilities. In this mini-review, the physiopathological relevance of CD4 T cell-driven activation in the presence of IL-1 family members will be discussed.

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INTRODUCTION

Naïve CD4 T cells can differentiate into effector or regulatory subsets, which will shape the quality and magnitude of adaptive immune responses^[1]. Each CD4 T cell subset exhibits specialized functions *in vivo* that are determined by the transcription factors they express and the cytokines they secrete. The induction of the distinctive patterns of gene expression in CD4 T cell subsets is dictated by their interaction with the antigen-presenting cells (APC) and also the cytokines present in their environment during T cell activation. The variety of effector responses elicited by CD4 T cell subsets, endows the host with abilities to respond to different types of pathogens.

The ability of naïve CD4 T cells to differentiate into specialized variants was initially reported 30 years ago by Mossmann and Coffman who demonstrated the existence of two types of murine T helper clones, designed as Th1 and Th2, differing in their profiles of lymphokine activities^[2]. Th1 cells secrete IFN γ and IL-2, and are responsible for cell-mediated immunity, including delayed-type hypersensitivity, which relies on macrophage activation. They are also responsible for both phagocyte activation and the production of opsonizing and complement-fixing antibodies by B lymphocytes. Th1 cells therefore critically contribute to defense against intracellular pathogens^[3]. Th2 cells secrete interleukin (IL)-4, IL-5 and IL-13 cytokines and skew the immune response toward humoral immunity. They induce IgE class switching by B lymphocytes and favor the activity of eosinophils. They are effective in the protection against helminthes^[4]. The differentiation of CD4⁺ T cells into Th1 or Th2 subsets can be replicated *in vitro* by adding IL-12 or IL-4, respectively, to cultures of naïve T lymphocytes activated by their specific clonogenic antigen presented by APC like dendritic cells^[5]. Interestingly, IFN γ produced by Th1 cells inhibits Th2 differentiation while IL-4 produced by Th2 cells inhibits Th1 differentiation^[5]. Under physiological conditions, differentiated Th1 or Th2 cells can be regarded as stable cells^[1].

Since the initial description of the Th1/Th2 dichotomy other subsets of CD4 T cells that suppress immune responses have been characterized including Foxp3 regulatory T cells (Tregs), which express the Foxp3 transcription factor, and IL-10-secreting Tr1 cells that rely on the transcription factors c-Maf and AhR for their development^[6,7]. These two T cell subsets are essential to prevent excessive autoimmune responses and maintain host homeostasis.

In 2005 a new subset of CD4 helper T cells characterized by an abundant production of the IL-17A (also called IL-17) cytokine was identified and named Th17 cells^[8]. Differentiation of Th17 cells from cultures of naïve mouse T cells was initially shown to be driven by the combination of the cytokines transforming growth factor (TGF)- β and IL-6^[9]. It was subsequently shown that these cells, which rely on the transcription factor ROR γ t for their development^[10], contribute to host defense against fungi. However, due to their secretion, besides IL-17A, of other proinflammatory mediators, including IL-17F, TNF α , GM-CSF and IL-22, dysregulated Th17 cell responses can also promote tissue inflammation *in vivo*^[11].

Another subset of T helper CD4 T cells, Th9 cells, which can be differentiated from naïve CD4 T cells in the presence of TGF β and IL-4, was characterized in 2008 by the groups of Kuchroo and Stockinger as CD4 T cells lacking Foxp3 but secreting high levels of the cytokine IL-9^[12,13]. Th9 cells can be induced *in vitro* from naïve T cells in the presence of TGF β and IL-4 or derived from Th2 cells "reprogrammed" into Th9 cells by TGF β ^[13]. Subsequent studies identified in 2010 PU.1 as the transcription factor responsible for Th9 cell development^[14]. A characteristic of the Th9 phenotype is its plasticity, as illustrated by their ability to convert to IFN γ -secreting cells in the context of autoimmune diseases and asthma (reviewed in^[15]). Nevertheless, Th9 cells feature a stable phenotype in cancer (reviewed in^[16]). Another characteristic is the skin-tropism of Th9 cells that can contribute to their scarcity in the gut or circulation of healthy subjects^[17]. The *in vivo* functions of Th9 cells are still being deciphered but it is clear that these cells promote inflammation in the context of colitis, asthma and experimental autoimmune encephalomyelitis (EAE), the mouse model for human multiple sclerosis^[15]. Furthermore, both mouse and human studies indicate that Th9 cells also contribute to host defense against parasites, possibly due to their IL-9 secretion^[15]. Recently, Th9 cells were also shown to exhibit potent anticancer properties upon adoptive transfer *in vivo*^[16,18-20].

The differentiation of T cells into polarized subsets not only depends on the engagement of TCR signaling and the costimulatory signals but also on the presence of cytokines in the environment of differentiating T cells as discussed above. While polarized CD4 T cell subsets are now routinely obtained *in vitro* from naïve T cells in the presence of a relevant cytokine combinations such as TGF β associated with IL-6 or IL-4 for mouse

Th17 and Th9 cells, respectively, as discussed above, these cocktails should not be considered as representative conditions of natural Th17 or Th9 cell differentiation *in vivo*; nor as excluding the role of other cytokines in CD4 T cell differentiation. In this regard, many proinflammatory cytokines present *in vivo* in inflammatory or cancer settings will affect T cell development and shape T cell functions. In the present review, we will summarize information on the effect of cytokines belonging to the IL-1 family on CD4 T helper cell differentiation with a focus on the contribution of these cytokines to the differentiation of recently discovered Th17 and Th9 subsets. The physiological and clinical consequences of IL-1-driven alteration of CD4 T cell biology will also be discussed.

INTERLEUKIN-1 CYTOKINE FAMILY

IL-1 β is, with IL-1 α the original member of the IL-1 family that currently comprises 11 members including IL-18 and IL-33^[21-23]. IL-1 α and IL-1 β act on a same receptor; the IL-1 type 1 receptor (IL-1RI). Another member of the IL-1 family, IL-1 receptor antagonist (IL-1Ra), competitively binds to IL-1RI but without activating it and consequently is a natural inhibitor of IL-1 α and IL-1 β . IL-1 β is primarily secreted by activated macrophages and dendritic cells but is also released by B cells and NK cells upon stimulation. IL-1 β is synthesized by these cells as an inactive precursor that has to be cleaved to an active mature cytokine by caspase-1 contained in multimeric complexes, the inflammasomes, activated during processes such as infections, autoimmunity or tumors^[24]. Released IL-1 β constitutes a soluble circulating cytokine that signals through the TIR domain of its receptor, IL-1RI, leading to the recruitment of the adaptor protein myeloid differentiation protein 88 (MyD88), the activation of NF- κ B signaling and the induction of several pro-inflammatory genes. In contrast to IL-1 β , IL-1 α is not secreted but remains attached to the membrane of the producing cells that include not only myeloid cells but also epithelial and endothelial cells^[23]. Consequently its effect is localized, contrasting with the diffuse, hormone-like effect of IL-1 β . Like IL-1 β , two other components of the IL-1 family, IL-18 and IL-33 were reported to act directly on T lymphocyte differentiation. IL-18 and IL-33 are widely expressed among epithelial cells constituting barriers in the gut, the lung and the skin. IL-18 is also expressed in myeloid cells, notably in antigen presenting cells such as dendritic cells and macrophages, whereas IL-33 is expressed in endothelial cells. Like IL-1 β , IL-18 requires proteolysis by caspase-1 to be activated and released from an inactive precursor, while IL-33 does not requires this proteolytic step as its proform is fully active, and is preferentially released from damaged necrotic or dead cells as a danger signal^[25]. Activated IL-18 acts through its specific receptor, IL-18R, while IL-33 acts through its specific receptor ST2 (known also as IL-33R or T1ST2),

both IL-18R and ST2 belonging to the IL-1RI receptor family. While the involvement of IL-1 in inducing inflammation has been documented for more than 30 years, the effects of IL-1 family cytokines on the differentiation of CD4 T cell subsets are still being the subject of intense investigation, as discussed below.

EFFECT OF IL-1 CYTOKINES ON NAÏVE AND ON TH1 AND TH2 EFFECTOR T LYMPHOCYTES

IL-1 β induces proliferation and maturation of thymocytes and naïve T lymphocytes with the help of thymic accessory cells or their product, IL-7^[26,27]. IL-1 β acts as an adjuvant, enhancing antigen-driven expansion and differentiation of naïve and memory CD4 T cells^[28]. An effect of IL-1 β on mature Th1 and Th2 cells was the subject of controversy. It was initially established that Th2 cell lines expressed the IL-1RI receptor that is required for a direct effect of IL-1 β on these cells, whereas this receptor was not detectable on Th1 cell lines, that restricted the IL-1 β target to Th2 lymphocytes^[29,30]. While an effect of IL-1 on T cells was initially investigated by determining its effect on the proliferation of mouse Th1 or Th2 clones, the quantification of signal cytokines was more recently preferred for determining the influence of IL-1 family cytokines on T cells. Using this criterion, it was found that the chief activators of signal cytokine production by Th1 or Th2 lymphocytes were not IL-1 β but rather two other members of IL-1 family, IL-18 and IL-33^[31-33]. The IL-18 receptor IL-18R was not detectable on naïve T cells, but was progressively expressed on differentiating Th1 cells, allowing IL-18 to promote cell proliferation and survival, and production of IFN γ (Figure 1A). The IL-33 receptor, ST2, is selectively expressed on Th2 cells. If Th2 cell lines are known to express IL-1RI, they express also predominantly ST2^[31]. ST2 is not expressed on naïve, regulatory and Th1 lymphocytes^[34]. ST2 allows IL-33 to enhance production of type-2 cytokines, in particular IL-5 and IL-13 by Th2 cells where it plays a major role in determining the Th2 phenotype compared with the IL-1RI receptor expressed on the same cells (Figure 1B). Consequently, IL-18 and IL-33 appeared as cytokines strictly specialized for Th1 and Th2 differentiation, respectively^[33]. Further analyses showed however that IL-18 not only activates Th1 cells for producing IFN γ , but also Th2 cells through their ST2 receptor for releasing type-2 cytokines notably IL-5 and IL-13. Similarly, IL-33 can activate its ST2 receptor, but also the IL-18 receptor IL-18R for enhancing IFN γ release^[33]. The common response to IL-18 and IL-33 was unexpected since IL-18R and ST2 receptors are respectively restricted to Th1 and Th2 cell lines. An explanation for this crossed reactivity could be the structural similarity between IL-18 and IL-33 that could permit a binding of each cytokine to both receptors.

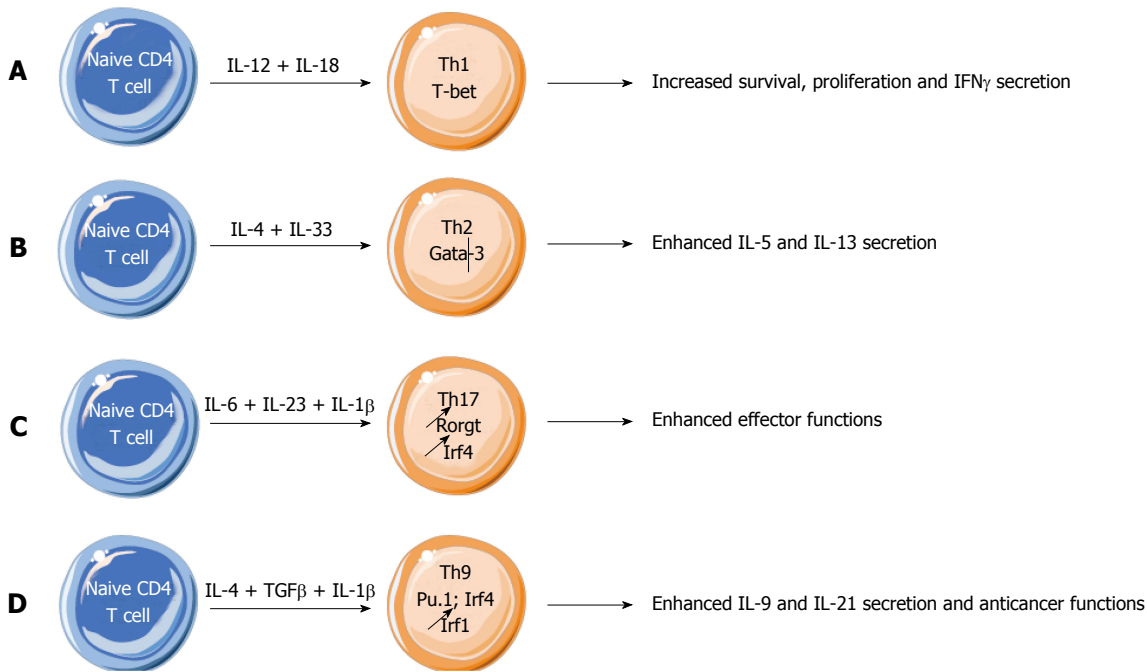


Figure 1 Effect of interleukin-1 family members on effector CD4 T cell differentiation. A: Interleukin (IL)-18 promotes Th1 cell proliferation and survival, and production of IFN γ ; B: IL-33 enhances Th2 cell differentiation and function, notably because of IL-33 driven increase of Th2-derived cytokines IL-5 and IL-13; C: IL-1 β critically supports Th17 cell differentiation by maintaining the expression of IRF4 and ROR γ t, two key transcription factors necessary for Th17 cell development and functions; D: IL-1 β enhances the expression of IRF1 in differentiating Th9 cells, leading to enhanced differentiation and effector functions of Th9 cells.

Consequently, IL-18 and IL-33 should be considered as Th1- and Th2-oriented, rather than Th1- and Th2-specific cytokines, respectively^[33] (Figures 1A and B).

In spite of the predominance of IL-18 and IL-33 receptors, IL-1RI receptor is important for the induction of Th2 cell immunopathology. In experimental asthma induced in the mouse, airway hypersensitivity responses to inhalation of ovalbumin were decreased in IL-1 α - and IL-1 β -deficient mice, while they were exacerbated in mice deficient in IL-1Ra^[35,36]. The Th2 cell response mediated resistance to a gastrointestinal nematode was also dependent on the presence of IL-1 α - and IL-1 β lymphocytes, demonstrating the role of IL-1 in parasite elimination, an important function of Th2 cells^[37].

EFFECT OF IL-1 β CYTOKINE ON TH17 LYMPHOCYTES

While mouse Th17 cell differentiation was initially believed to solely rely on TGF β and IL-6, it was clearly demonstrated that proinflammatory cytokines like IL-1 β and TNF α could shape Th17 cell differentiation as well^[38]. IL-1 β was subsequently identified as a major actor in the physiology of Th17 cells, as illustrated for instance by its requirement for the development of Th17 cell-sustained autoimmunity like in EAE^[39,40] (Figure 1C). IL-1 regulates the expression of IRF4 and ROR γ t, two transcription factors required for Th17 differentiation^[40] (Figure 1C). Compared with Th1 and Th2 cells, mouse Th17 lymphocytes strongly express

IL-1RI, the mandatory receptor for IL-1 α and IL-1 β ^[40]. This high expression of IL-1RI on murine Th17 cells is similar to the heightened expressions of IL-18R on Th1 cells and the heightened expression of ST2 on Th2 cells. Neither IL-18 nor IL-33 alone or in combination with STAT3 activators had any effect on IL-17 production^[31].

IL-1RI is expressed on approximately 20% of CD4⁺ T cells in healthy human peripheral blood. The frequency of IL-1RI⁺ cells was higher (26%) in the memory CD4⁺ T-cell subset but IL-1RI⁺ cells were also present (15%) in the naive subset even though they were absent from human umbilical cord blood. This suggests that IL-1RI expression in naïve CD4⁺ T cells is induced at the periphery, likely through exposure to cytokines such as IL-7 or IL-15 and to TCR triggering^[41]. Compared with IL-1RI-negative memory CD4⁺ T cells, IL-1RI⁺ memory CD4⁺ T cells produced higher levels of IL-17 in response to TCR triggering and this response was further increased in the presence of IL-1 β . TCR activation and cytokines such as IL-7, IL-15 and TGF β induced IL-1RI expression, allowing IL-1 β to promote IL-17 production from initially IL-1RI-negative CD4⁺ T cells^[41]. It is also noteworthy that human Th17 cells were proposed to originate from regulatory T cells (Tregs) differentiated in the presence of IL-2 and IL-1 β ^[42]. In line with this, IL-1RI expression on human CD4⁺ T cells represents an intermediate in the differentiation of Th17 from Tregs^[43].

IL-23 is a critical cytokine in determining Th17 cell functions, as illustrated by early reports suggesting the lack of pathogenicity of TGF β and IL-6- derived

Th17 cells in the context of EAE^[44]. Importantly, it was reported that mouse Th17 cell differentiation can proceed in the absence of TGF β but in the presence of IL-6, IL-23 and IL-1 β ^[45]. These cells were found to coexpress ROR γ t and T-bet, secrete IL-17 and IFN γ and are pathogenic *in vivo* in contrast to Th17 cells differentiated with TGF β . In line with this, we noted that TGF β and IL-6 favor the expression of two ectonucleotidases, CD39 and CD73 through down-regulation of the transcriptional repressor Gfi-1. The conjugated effect of these two nucleotidases is the production of immunosuppressive adenosine from ATP degradation. Differentiation of Th17 cells in the absence of TGF β results in their lack of expression of ectonucleotidases. Accordingly, substitution of IL-1 β to TGF β for IL-17 cell generation leads to T cells with maintained anti-tumor cytolytic activity and higher capacity to delay tumor growth upon adoptive transfer^[46,47].

EFFECT OF IL-1 CYTOKINES ON TH9 LYMPHOCYTES

Relatively to Th1, Th2 and even Th17 CD4 T cells, the Th9 subset was only recently characterized, first in mouse in 2008 then in humans in 2010. Its scarcity in healthy conditions explains the difficulty for collecting large number of Th9 cells, except through culture experiments in the presence of IL-4 and TGF β for inducing Th9 polarisation of human or mouse naive CD4⁺ T cells. A study of the effects of IL-1 family cytokines on IL-9 expression by mouse CD4 T lymphocytes demonstrated that IL-1 β , but also IL-1 β , IL18 and possibly IL-33, could enhance IL-9 expression, even in the absence of IL-4, but only in the presence of TGF β ^[48]. Stimulation of CD4 T cells by IL-1 β and TGF β induced a larger IL-9 expression than did the mixture of IL-4 and TGF β conventionally used for inducing Th9 polarisation, and this response persisted even when induced by T cells from IL-4 KO mice^[48]. Using human CD4 T cells, Wong *et al.*^[49] also reported that IL-1 β enhances Th9 cell differentiation performed *in vitro* from naive CD4 T cells polarized in the presence of TGF β and IL-4. In our laboratory we have further explored the direct effects of IL-1 family cytokines on IL-9 expression from differentiating mouse Th9 cells derived from naïve CD4 T cells^[18]. While we found no significant effect of IL-1 α , IL-18 or IL-33 addition on IL-9 secretion from CD4 T cells derived under Th9-skewing conditions, IL-1 β not only increased IL-9 expression but also drove the secretion of another cytokine, IL-21 from Th9 cells^[18]. We found that IL-1 β engaged the IL-1R1 receptor on differentiating Th9 cells, leading to the activation of MyD88-dependent intracellular signalling that induced the activation of the tyrosine kinase Fyn. This series of events led within 15 min after the beginning of the differentiation to the phosphorylation of the transcription factor

STAT1, which ultimately bound to the IRF1 promoter and favoured IRF1 expression^[18]. Subsequently, IRF1 bound to the promoters of the *I/9* and *I/21* genes and enhanced secretion of the corresponding cytokines by Th9 cells^[18].

IL-21 is a pleiotropic cytokine produced primarily by natural killer T cells, T follicular helper cells and Th17 cells^[50]. An IL-9-dependent antitumor effect of conventionally differentiated Th9 cells adoptively transferred was previously observed in mouse bearing B16-F10 melanoma or Lewis lung carcinoma^[19,20]. The antitumor activity of Th9 lymphocytes was inhibited by a neutralizing anti-IL-9 antibody. The cellular mechanisms of this antitumor effect remained elusive as the role of mast cells and CD8 cytotoxic T cells was disputed^[19,20] (and reviewed in^[16]). We observed that Th9 cell antitumor activity was considerably increased when the adoptively transferred Th9 cells had been differentiated in the presence of IL-1 β (Figure 1D). In contrast to conventionally differentiated Th9 cells, the antitumor activity of adoptively transferred Th9 cells differentiated in the presence of IL-1 β was not dependent on IL-9 but was abrogated by a neutralizing anti-IL-21 antibody^[18]. IL-21 acted by enhancing the activity of tumor-infiltrating and tumor-associated NK and CD8 cytolytic cells. Importantly, in this context of tumor, Th9 cells differentiated in the presence of IL-1 β were stable, maintaining for several days expression of IL-9 and IL-21 in tumor tissues without acquiring the markers of transdifferentiation into Th1, Th2, Th17 or Treg markers^[18]. Consequently, and also through their tropism to tumor tissues, Th9 cells differentiated in the presence of IL-1 β could presumably constitute an interesting tool for cancer immunotherapy^[16,18].

CONCLUSION

Since the discovery of the lack of IL-1RI on mouse Th1 cells, many studies focused on *in vivo* animal models of Th2 related diseases. Different models of mice either deficient for IL-1 α /IL-1 β or for their receptor IL-1RI were analyzed to determine the effects IL-1 family members on the Th2 response; and most, but not all, of these studies agree with the idea that both IL-1 α and IL-1 β promote proliferation and differentiation of Th2 cells *in vitro* and *in vivo*. Surprisingly few studies have investigated the effects of IL-1 on human Th2 cells, and the findings do not enlighten if human Th1 or Th2 cells express a functional IL-1RI and therefore can be modulated by IL-1 α or IL-1 β cytokines. Furthermore, recent studies demonstrated that the major IL-1 family cytokines directly acting on Th1 and Th2 cells are IL-18 and IL-33 rather than the classical IL-1 α and IL-1 β .

In contrast to the discrepant results obtained with Th1 and Th2 cells, animal models and human studies all agree with the concept that IL-1 β has a fundamental role in Th17 modulation. The *in vitro* assays clearly demonstrate that IL-1 β is able to induce the

transcription factors necessary for Th17 development, as soon as its own receptor IL-1RI is upregulated in naïve T cells upon TCR triggering in the presence of γ -chain cytokines. IL-1RI expression is maintained on effector Th17 cells and this signaling is probably responsible for the prolonged survival of these cells during inflammation. This IL-1-driven enhanced Th17 cell activity has *in vivo* relevance. Nakae *et al.*^[51] have shown in a mouse model of arthritis that IL-1 drives the secretion of IL-17 from CD4 T cells, resulting in enhanced arthritis development^[51]. These findings have possible clinical relevance given the ability of IL-1 neutralization using Anakinra, a recombinant version of IL-1Ra, to alleviate the symptoms of rheumatoid arthritis^[52]. However, whether the beneficial effect of IL-1Ra administration in inflammatory diseases results from the inhibition of Th17 responses remains elusive. In a cancer setting, we have shown that the treatment of tumor-bearing mice with the chemotherapeutic agent 5-fluorouracil leads to the *in vivo* release of IL-1 β , the release of IL-17 from CD4 T cells and tumor progression^[53]. Importantly, neutralization of IL-1 β with IL-1Ra *in vivo* led to synergistic anticancer effects upon combination with 5-FU in mouse models. A clinical trial evaluating the possible benefit of IL-1Ra addition to 5-FU treatment in metastatic cancer patients is ongoing (NCT02090101). Thus, IL-1Ra-driven down-modulation of Th17 cell responses may be clinically relevant for the treatment of cancer and inflammatory diseases.

Finally, we found that IL-1 β was able to enhance the differentiation of mouse naïve CD4⁺ T cells into Th9 cells by considerably enhancing expression of IL-9 and IL-21 cytokines and efficiency of antitumor activity in several models of mouse tumors through CD8⁺ and NK cells. While we found in a mouse model of melanoma that the systemic administration of IL-1 β enhanced the anticancer efficacy of adoptively transferred Th9 cells^[18], these findings may be difficult to translate in the clinic because of the high toxicity profile of IL-1 administration in humans. We believe instead that our findings may be relevant in the context of adoptive T cell therapy with Th9 cells treated with IL-1 β *in vitro* and given in combination with chemotherapy and/or immunomodulators. Thus, it will be important to determine if comparable IL-1 β -modified Th9 cells can be obtained from human T lymphocytes, and if their antitumor activity could be even more increased by association with immune checkpoint inhibitors like PD-1, and whether appearance of autoimmune side effects could be a limitation for their use in cancer therapy.

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