Introduction

The “Hallmarks of Cancer” describe a number of important characteristics that are required for the transformation of normal cells to malignant cells and tumor-promoting inflammation. Infiltrating inflammatory cells in the tumor microenvironment produce various growth factors and cytokines that sustain the proliferation of cancer cells, allowing them to resist cell death, and promote invasion and metastasis. Among these host-immune cells, T helper (Th) 17 cells that produce interleukin (IL)-17A are of importance because IL-17A has a wide variety of biological functions, especially related to inflammation and the resultant carcinogenesis, as well as immune suppression in patients with cancer. IL-17A is the most widely studied member of the IL-17 family, and was demonstrated to play a critical role in host defense against various microbial pathogens, as well as against tissue inflammation.

While the role of IL-17A has been explored extensively in inflammatory diseases, its function in malignant diseases remains to be fully defined. Here, we review the immunological mechanisms of IL-17 in cancer, and discuss the potential therapeutic strategy of IL-17 inhibition.

IL-17A

IL-17A, often referred to as IL-17, was originally discovered at transcriptional level. Human and mouse IL-17A were later cloned, and it was demonstrated that IL-17A is a major vehicle by which T cells communicate with the hematopoietic system and signal to bone marrow stromal cells to produce G-CSF (granulocyte-colony stimulating factor) that support the differentiation of hematopoietic cells to the granulocyte lineage. Subsequent studies showed that IL-17A is produced in several types of cells, and in 2005, Th17 cells could be derived from naive CD4+ T cells under the control of transforming growth factor (TGF-β) and IL-6, and became one of the major sources of IL-17A. It was then demonstrated that STAT3 and RORC play critically roles in Th17 lineage commitment in mice and humans.

A receptor for IL-17A (IL-17RA) was first isolated and cloned in mouse thymoma cells, and bioactivity of IL-17A was confirmed in that same study. IL-17RA is a member of the IL-17 receptor family, which includes IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE, and pairs with IL-17RC to allow binding and signaling of IL-17A and IL-17F.
IL-17 in Host Defense, Microbiota, and Carcinogenesis

IL-17A is predominantly expressed by adaptive immune cell populations, including Th17 cells, cytotoxic T-cells, invariant NKT cells, and γδT cells. Th17 cells belong to a subset of Th cells, characterized as producers of tumor necrosis factor (TNF) α and IL-17, which represent a family of cytokines of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, in addition to producing IL-6, IL-21, IL-22 and IL-23. Th17 cells are thus considered new lineage of Th cells that play a key role in host defense against many infectious agents by mediating effector mechanisms through their cytokines. Recently, the discovery of innate lymphoid cells (ILCs) has shown that IL-17A can also be produced by ILCs and lymphoid tissue inducer-like cells. Additionally, non-immune cells such as Paneth cells are able to secrete IL-17A.

Furthermore, Th17/IL-17A are also associated with chronic inflammatory diseases, autoimmune disorders, and cancer.

IL-17 in Host Defense, Microbiota, and Carcinogenesis

The primary function of IL-17A seems to be controlling the gut microbiota as well as the clearance of extracellular bacteria and fungi.

The signaling of IL-17A coupled with IL-17 receptor has been shown to play a protective role in host defenses against many bacterial and fungal pathogens. However, IL-17A appears not to be protective against viral infections such as influenza.

The use of mouse models for colon cancer has provided evidence for interactions among innate and adaptive mucosal immune responses and colonic microbiota in colonic carcinogenesis. However, it is not clear which members of the microbiota or which mucosal immune responses might promote colon cancer. Interestingly, IL-17A has been thought to be a strong candidate to promote inflammatory immunological responses leading to carcinogenesis.

The concept that microbe-induced IL-17A mucosal adaptive responses can be carcinogenic is supported by the observation that Helicobacter-Pylori-associated gastritis, which precedes most cases of gastric cancer, requires IL-17A. However, studies are still underway to identify bacteria that induce IL-17A production in the human gastrointestinal lesion. It has recently been suggested that mucosal Th17 cell-mediated immune responses require microbe-associated molecular patterns and physical proximity of the microbe to the epithelial cells.

IL-17 in Autoimmune Diseases

Th17 cells have been studied extensively in the past decade and have been shown to associate with the pathogenesis of many experimental autoimmune diseases and human inflammatory disorders. The continuing studies suggested that IL-17A-producing cells, including Th17 cells, are involved in human psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma. Although many studies have reported that Th17 is the major source of IL-17A, non-lymphoid cells including mast cells and neutrophils also may produce IL-17A, since most of these conclusions are based on immunohistochemistry staining, which does not discriminate between IL-17A-producing cells and cells bound to IL-17A due to the ubiquitous expression of IL-17RA.

Multiple sclerosis is a neurological disease caused by immune cells which attack and destroy the myelin sheath that insulates neurons in the brain and spinal cord. This neurological disorder and its animal model have historically been associated with Th17 discovery. In addition, elevated IL-17A expression in disease lesions, as well as increased levels of IL-17A in peripheral blood, were reported previously prior to the discovery of Th17.

Psoriasis, autoimmune-inflammatory skin disease, is characterized by the infiltration of many types of immune cells, including massive infiltrating CD4+ cells, dendritic cells, cytotoxic T cells and neutrophils in the dermis and epidermis. Since the high production of interferon (IFN)-γ, TNF-α and IL-12 was present, psoriasis was recognized as a Th1-driven disease. However, it was recently suggested that Th17 cells may synergize with Th1 cells in driving pathologic pathway in the disease after IL-17A and Th17 were discovered.

In rheumatoid arthritis, a chronic autoimmune-inflammatory disease with chronic joint inflammation that leads to destruction of cartilage and bone, IL-17A levels in the synovium have been reported to be strongly correlated with tissue damage. Direct clinical significance of IL-17A in rheumatoid arthritis was reported in recent clinical trials that found that two anti-IL-17A antibodies, namely secukinumab and ixekizumab, were significantly beneficial to these patients in clinical trials.

Crohn’s disease and ulcerative colitis, two major types of inflammatory bowel disease (IBD) in human, have also been linked to IL-17A and Th17. According to Monteleone I et al., massive Th-17 cells infiltrate inflamed tissue of IBD disease and the levels of IL-17A were elevated in patients with IBD. However, recent clinical studies targeting IL-17A were negative and increased adverse events were observed in the treatment arm.

IL-17A in Cancer

The pathogenic and non-pathogenic features of Th17 cells in cancer remain controversial, and Th17 cells appear to promote disease progression in hepatocellular carcinoma and gastric cancer. Th17 cells have also been reported to be present in the vicinity of malignancies including ovarian, gastric, colorectal, breast, pancreatic carcinomas and melanomas.
IL-17A can enhance tumor growth in vivo through the induction of IL-6, which in turn activates oncogenic transcription factor signal transducer and activator of transcription 3 (STAT3), and upregulates pro-angiogenic genes in tumors. IL-17A also facilitates development of colorectal carcinoma by fostering angiogenesis via promotion of VEGF production by tumor cells. However, the exact role of IL-17 in angiogenesis has yet to be determined.

Immunosuppressive myeloid cells were previously described in cancer patients several times, although their functional significance in the immune system has only recently been evaluated. Accumulating evidence suggested that a population of cells with suppressive activity, referred to as MDSC (myeloid-derived suppressor cells), may contribute to the negative regulation of immune responses during cancer and patients' conditions. We have previously characterized circulating numbers of MDSC in patients with various types of cancers, and reported that increased production of IL-17A was correlated with immune suppression involving MDSC, as well as with malnutrition in patients with various types of cancer.

In patients with breast cancer, tumor aggressiveness was reported to be enhanced by IL-17A via induction of angiogenic factors such as chemokines and VEGF (vascular endothelial growth factor). We previously reported that IL-17A production and VEGF serum levels were also increased in advanced-stage breast cancer. The production of IL-12, which induces Th1 cells and maintains cell-mediated immune reaction, and the proliferation of lymphocytes (SI: stimulation index), a marker of cell-mediated immune function, were both shown to decrease along with disease advancement. Moreover, the production of IL-17A by Th17 and the VEGF levels were both positively correlated with the levels of MDSC, neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) which are both good parameters of inflammation, and were inversely correlated with IL-12 production and SI.

Fig. 1 Correlations of interleukin (IL)-17 production with various immunological parameters. Production of IL-17 was positively correlated with VEGF serum levels (1a), circulating numbers of MDSC (1b) and the NLR (1c), and inversely correlated with the SI (1d) and IL-12 production (1e). VEGF: vascular endothelial growth factor, MDSC: myeloid-derived suppressor cells, NLR: neutrophil-to-lymphocyte ratio, SI: stimulation index.
have been reported by our laboratory, and these strong correlations among immunosuppression, inflammation and malnutrition involving MDSC, IL-17A, and VEGF, seemed to be present in advanced malignant diseases. These data suggest that the axis of IL-17A, MDSC, and VEGF may be activated further in advanced diseases when nutritional impairment is present. Taken together, this axis is closely related with nutritional status, and appears to play a key role in the development of cancer cachexia.

Inhibition of IL-17A as a Therapeutic Approach for Cancer

The therapeutic inhibition of Th17-associated cytokines may be of benefit in oncology. IL-17A, IL-22, and IL-23 may be the target cytokines, and for IL-17A, secukinumab and ixekizumab represent two FDA-approved IL-17A inhibitors. However, no clinical trials have been conducted so far for these agents in a cancer setting. Other antibodies against IL-17A, ustekinumab and brodalumab, have also been developed and proven to be safe to use.

Other than the monoclonal antibodies, highly specific and potent inhibitors targeting Th17 specific transcription factor RORγt have been identified and found to be highly effective.

Concluding Remarks

Th17 cells are essential for the clearance of extracellular pathogens including fungi and bacteria at skin and mucosal barrier surfaces. Th17 differentiation is complex and implies a series of positive and negative regulators that can be therapeutically targeted. An increasing number of diseases have been linked to IL-17A and Th17 cells, and their specific contributions to disease pathogenesis are being revealed. Both pre-clinical research and clinical trials are underway to test these concepts. Several strategies utilizing inhibition of Th17 and IL-17A have arisen, and the clinical trials of these complexes are still at an early stage. Currently this is a general hope for clinical development in oncology. It should be specific to the current review.
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