Impact of IL-17 on Cells of the Monocyte Lineage in Health and Disease

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Abstract: Discovered in 1993, IL-17 has been the focus of intensive research during the last decade, in particular because of its neutrophil-accumulating capacity in several mammalian organs. We now know that the IL-17 family includes at least 6 members, of whom at least IL-17A and IL-17F can be produced by T cells. Thus, IL-17 is positioned at the interface of acquired and innate immunity and constitutes a link between T cell activity and the accumulation of neutrophils locally in organs. Interestingly, there is accumulating evidence that IL-17 has effects on myeloid cells other than neutrophils as well, namely on cells of the monocyte lineage. This review article scrutinizes the evidence that IL-17 exerts a functional impact on the cytokine production and functional activity in cells of the monocyte lineage in health and disease. Notably, this evidence includes data suggesting that there are conditions in which cells of the monocyte lineage are likely to play a significant pathogenic role and where IL-17 is directly controlling the activity of these key effector cells.

Key Words: Macrophage, osteoclast, dendritic cell, APC, cytokine, inflammation, interleukin, antigen-presenting cell.

1. INTRODUCTION

A well-balanced cross-talk between the innate and adaptive immune systems ensures an adequate response to microbial pathogens and harmful auto-antigens. In principle, the innate immune system initiates and controls the subsequent adaptive immune response. Cells of the monocyte lineage, such as macrophages and dendritic cells (DC) can serve as antigen presenting cells (APC) and thereby bridge innate and adaptive immunity. The recognition of specific antigens results in the up-regulation of co-stimulatory molecules in APC, providing the signal necessary for the proliferation of specific effector T cell clones and their subsequent activation. Importantly, cells of the monocyte lineage constitute important source of cytokines; cytokines that participate in orchestrating the adaptive inflammatory response. In addition, macrophages are also potent phagocytes [1].

Once the adaptive immune response is switched on, the induced production of chemokines, growth factors and other mediators leads to the functional coordination of effector cells, including phagocytes and APC. Thus, within both the innate and the adaptive immune responses, there is a “tight” cross-talk between T cells and cells of the monocyte lineage. Notably, accumulating evidence now suggests that the homodimeric cytokine interleukin (IL) -17 may play an important role in this type of communication [1,2]. Discovered in 1993 by Rouvier and co-workers [3], IL-17 has been focus of intensive research over the last decade. Currently, the IL-17 family of cytokines includes 6 members (IL-17A, B, C, D F and A/F). One previous member of this cytokine family, IL-17E, has been renamed IL-25 because of its unique compared with the other known IL-17 family members functional role in eosinophil mobilization [2]. Until now, the vast majority of published studies on IL-17 have focused on the effects of IL-17 on the accumulation and activity of neutrophils, exerted mainly through the induced production and release of C-X-C chemokines, growth factors and IL-6 in various structural cells in several mammalian organs [2, 4]. Clearly, this research has generated considerable knowledge about the interplay between acquired and innate immunity. However, there are now several published studies that demonstrate effects of IL-17 on another myeloid cell lineage, the monocyte lineage, particularly monocytes and their progeny macrophages, osteoclasts and DC [5-7]. More specifically, most of these studies have addressed the effect of IL-17 on monocyte-derived cytokines and a limited number of studies only do describe additional, functional effects of IL-17 on monocytes and their progeny. However, there are disorders in which IL-17 has been attributed a pathogenic role and in which immune cells of the monocyte lineage are implicated as important effector cells [8,9]. This literature review summarizes current knowledge about IL-17’s impact on cells of the monocyte lineage in health and disease.

2. SOURCES OF IL-17

Currently, various T cell types are considered as an important source of IL-17 and there is a distinct T helper cell subpopulation, Th-17, that has been the focus of much research recently [5, 10-12]. Notably, the polarization of naïve T helper cells towards the Th-17 subtype display some species differences and this issue has been more extensively reviewed elsewhere [4]. Briefly, in mice, the polarization depends on T-cell receptor (TCR)-signaling and the presence of transforming growth factor (TGF)-β and IL-6. TGF-β and IL-6 are believed to induce the expression of the Th-17 archetype transcription factor retinoid-related orphan receptor (ROR) γ as well as the expression of the inducible chain of the receptor for IL-23. IL-23, in turn, is an up-stream regula-

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Fig. (1).


tor of IL-17A production by Th-17 cells and may also be important for extending the survival of Th-17 cells. More recent data suggest that IL-6 is important for inducing the production of IL-21; a cytokine that promotes the differentiation of Th-17 cells in an autocrine manner. There are factors inhibiting Th-17 cell differentiation as well, including interferon (IFN)-γ, IL-4, and IL-2. In humans, the critical difference compared with mice seems to be that the role of TGF-β is more ambiguous.

As indicated in currently available publications, the hallmark of Th-17 cells is the production of IL-17A, its sibling IL-17F and the antibacterial cytokine IL-22 [4,13,14]. However, additional subsets of T cells may produce IL-17 as well [2,4]. Early studies indicated that IL-17 producing T cells can be of the Th-1 and Th-2 phenotype [15, 16]. In addition, it has been claimed that IL-17A is expressed by eosinophils and neutrophils, even though these findings in humans and mice, respectively, are in need of confirmation in functional studies [17, 18].

Some recent publications indicate that under certain physiologic or pathologic conditions, IL-17 can be also secreted by cells of the monocyte lineage. For instance, IL-17A mRNA and protein are expressed in human placental macrophages (Hofbauer cells) [19]. In Langerhans cell histiocytosis (LCH), DC and multinucleated giant cells express and secrete high quantities of IL-17A [20]. Moreover, recent study has shown that alveolar macrophages from patients with asthma contain markedly more intracellular IL-17A protein than the same cells from normal control subjects do; this is associated with a corresponding difference in the concentration of extracellular IL-17A in bronchoalveolar lavage fluid [21]. In a mouse model of allergic asthma, CD11b+F4/80+ alveolar macrophages are the main producers of IL-17A in the lung [21]. In rodents, peritoneal macrophages express IL-17A upon in vitro stimulation with Porphyromonas gingivalis [22]. Also, the IL-17A “sibling” IL-17F can be secreted by activated human monocytes [23]. Another member of IL-17 family, IL-17E, is secreted by alveolar macrophages during particle-induced airway inflammation [24].

3. IL-17’S IMPACT ON CELLS OF THE MONOCYTE LINEAGE

3.1. IL-17 Receptors and Signal Transduction

Current studies have shown that IL-17A and IL-17F share the same receptor, the IL-17 receptor (IL-17R) A, which is expressed virtually by all cells [25, 26], including cells of monocyte lineage. It has been shown that human leukaemic monocytic cell line (THP-1) constantly express IL-17RA [27]. DC also express IL-17RA, as it has been demonstrated in mice bone marrow-derived CD11c⁺ cells [8].

The IL-17 family has at least five additional receptors, IL-17RB-E for which the functional interrelationship remains to be completely elucidated [2, 28]. Similarly to IL-17RA, receptor for IL-17B and IL-17E, IL-17RB, and IL-17C’ receptor IL-17RC are expressed by various tissues (reviewed in [2]). Clearly, the published data on expression of these receptors particularly by the cells of monocyte lineage is currently limited and requires further investigation. Nevertheless, it has been shown that upon stimulation with IL-4, TGF-β or IL-10 in vitro, monocyte-derived macrophages and
DC from healthy donors express membrane-bound and soluble IL-17BR [29].

The interaction between IL-17 and its receptors on various cells results in the up-regulation of several genes, which participate in tissue injury, inflammation and immune response [30, 31]. The signal transduction initiated by the ligation of IL-17R on monocytes includes tyrosine phosphorylation of Janus kinases (JAK)/Signal transducers and activators of transduction (STAT) proteins [32] and Ras-Raf/Mitogen-activated protein kinase (MAPK) pathways [33]. In human monocytic progenitor cell line (U937) and monocyte-derived macrophages recombinant (r) human (h) IL-17 induces rapid time-dependent stimulation of tyrosine phosphorylation of raf-1 serine/threonine kinase, JAK1, 2 and 3, Tyk 2 and STAT 1, 2, 3 and 4 [32-34]. Interestingly, it has recently been claimed that the down-stream, intracellular signaling of the IL-17 receptor includes a potentially unique adaptor protein, named Act1 [28].

3.2. IL-17' Effects on Cells of the Monocyte Lineage from Healthy Donors and Monocytic Cell Lines In Vitro

Recombinant hIL-17A induces the expression and protein synthesis of TNF-α, E2 (PGE2), IL-1β, IL-6, prostaglandin E2 (PGE2), IL-10, IL-12, IL-1R antagonist, and stromelysin from monocyte-derived macrophages [7], but have no effect on nitric oxide production by these cells. IL-4 and IL-10 abolished, whereas IL-13 and TGF-β partially inhibited IL-17' effect on the IL-1β release. While IL-10 substantially suppressed IL-17A-induced TNF-α release, IL-4, IL-13, and TGF-β2 decreased TNF-α secretion only partially [7]. Recombinant hIL-17A up-regulates monocyte COX-2 expression [38]. Recombinant hIL-17A also stimulates expression of matrix metalloproteinase (MMP) - 9 mRNA and protein production [39]. Stimulation of monocyte-derived DC with rhIL-17A yields a semi-mature, mixed monocytes/macrophage DC, which expressed CD14, CD68, CD1a, MHC-II and CCR6 and were CD40high [20].

In a human leukaemic monocytic cell line (THP-1), a cell line with macrophage-like properties, rhIL-17A induces PGE2-dependent TNF-α mRNA expression and protein synthesis [37]. In the same cell line rhIL-17B and C were more potent than IL-17A and induced significantly higher levels of TNF-α and IL-1β [40].

3.3. Haematopoiesis

Several studies have demonstrated haematopoietic activities of IL-17 [41]. In addition to the data suggesting that IL-17 stimulates granulocytopenia in vitro and in vivo, there is data on mice implying that IL-17A stimulates the production of monocytes. Thus, it has been demonstrated that overexpression of IL-17A in splenectomised mice results in a substantial increase in granulocyte-erythrocyte-macrophage-monocyte (GEMM) colony forming units (CFU), that is accompanied by a 10-fold increase in peripheral blood (PB) monocytes [42]. Adenovirus-mediated gene transfer of the murine IL-17A cDNA targeted to the liver also results in increase of GEMM-CFU [43].

In humans, another member of the IL-17 cytokines family, IL-17D, displays opposite effects and actually inhibits myelopoiesis: rhIL-17D inhibits the formation of granulocyte-macrophage (GM)-CFU and GEMM-CFU from bone marrow mononuclear cells [44]. Currently published data actually do not suggest that IL-17 should be considered as a potent growth factor for the cells of the monocyte lineage. New studies on pathological conditions linked to IL-17 and cells of the monocyte lineage are required to elucidate its potency more thoroughly.

3.4. Infection

Most studies on mice models indicate a protective role of IL-17 in host defense, and this impact may actually in part be due to IL-17' effect on cells of the monocyte lineage. The general pattern is that the production and release of IL-17A is induced in response to infections with bacterial and fungal pathogens. In line with this, it has been shown that Mycoplasma pneumonia infection increases the protein level of IL-17A and gene expression of IL-17A, IL-17C and IL-17F in lungs [45]. In experiments using IL-17A knock-out mice, local challenge with Klebsiella pneumoniae or systemic with Candida albicans, causes an impaired and delayed organ-specific myeloid host response, which results in a significantly reduced LD50 [46, 47]. During Cryptococcus neoformans infection in mice, over-expression of IL-13 results in diminished Th-17 responses, reduced survival time and higher pulmonary fungal load. The increased morbidity is closely associated with an alternative activation of macrophages, which results in a diminished fungicidal activity of macrophages [48, 49]. In a mice model of helminth Schistosoma mansoni infection, the inhibition of Th-17 responses is also associated with formation of alternatively activated macrophages [50]. The precise mechanism of induction of insufficient macrophage phagocytosis has not been addressed in these studies, however recent study in Bordetella Pertussis infection mice model suggests that IL-17 may play an active role in this process [51]. According to this study on Bordetella pertussis, stimulation of primary peritoneal macrophages or alveolar macrophages (MHS cell line) with IL-17A protein results in significant enhancement of the bactericidal activity of macrophages. Thus, IL-17A significantly enhanced the killing of Bordetella Pertussis and bacteria were undetectable in macrophages already 2 h after stimulation with IL-17A. Taking in account that progression of IL-17-linked diseases, such as asthma [52], chronic obstructive pulmonary disease [53] and cystic fibrosis [54] are associated with frequent and comparably more severe infections, IL-17' effects on the bactericidal activity of macrophages warrant further investigation.

3.5. Allograft Rejection

In humans, elevated IL-17A levels have been associated with organ graft rejection [55, 56]. IL-17' involvement in acute allograft rejection has been demonstrated in elegant rodent models of heart transplantation [8, 57, 58]. In a mice model, intraperitoneal administration of an IL-17 inhibitor (soluble IL-17R-Ig fusion protein) resulted in an approximately two-fold prolongation of heart grafts survival [8]. Similar results were observed, when IL-17R-Ig gene transfer was performed ex vivo into the donor hearts [58]. The increased survival of recipients was closely associated with a reduced infiltration of grafts cells of the monocyte lineage.
number of heart-infiltrating CD11b+ monocytes [9]. On the post-infectious autoimmune myocarditis, the neutralization of endogenous IL-17A with a specific antibody reduces the inflammation, monocytes constitute a substantial part of tissue; a recruitment that is associated with disease severity.

A few data sets from human patients have indicated that IL-17 is involved in chronic allograft rejection as well. In lung transplantation, chronic rejection takes the form of oblitative bronchiolitis (OB), which is characterized by fibrous lesions that occlude the terminal bronchioles [60]. Studies in rodent models indicate a critical role of autoimmunity against collagen type V in chronic lung allograft rejection [61]. Peripheral blood mononuclear cells (PBMC) from lung transplant recipients have been analyzed for the immunoreactivity against collagen type V over 7 years after primary lung transplantation [62]. This analysis has revealed that PBMC from lung transplant recipients induce collagen type V-specific trans-vivo delayed type hypersensitivity (TV-DTH). Indeed, it is possible to inhibit this phenomenon using anti-IL-17A, anti-TNF-α and anti-IL-1β antibodies. Notably, the removal of CD14+ monocytes or CD4+ T cells from this experimental system markedly inhibits TV-DTH to collagen V. Importantly, the referred data indicate that strong collagen type V-specific responses are associated with a substantially increased incidence and severity of OB [62]. Overall, the collagen type V-specific responses appear to be depending upon both CD4+ T cells and monocytes and do require the IL-17-induced production of the “classic” monocyte-derived pro-inflammatory cytokines TNF-α and IL-1β.

3.6. Autoimmune Myocarditis

The development of autoimmune myocarditis may also be associated with Th-17 responses [63,64]. In myocardial inflammation, monocytes constitute a substantial part of tissue-infiltrating cells [6]. Interestingly, in a mouse model of post-infectious autoimmune myocarditis, the neutralization of endogenous IL-17A with a specific antibody reduces the number of heart-infiltrating CD11b+ monocytes [9]. On the other hand, the addition of recombinant IL-17A protein enhances the myocarditis scores [9]. Thus, it seems as if IL-17A induces the recruitment of monocytes in to the heart; a recruitment that is associated with disease severity. This positions IL-17 as a potential pro-inflammatory cytokine in this condition.

3.7. Experimental Autoimmune Encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is a well-established experimental animal model for human multiple sclerosis; a chronic inflammatory disease of the central nervous system. EAE resembles multiple sclerosis in the sense that both conditions involve T cells and are characterized by inappropriate recruitment and activation of leukocytes in central nervous system causing oedema, demyelination, glial scaring and axonal injury. These lesions alter signal conduction in the peripheral nerves, which contributes to disabling neurological deficits. In EAE, macrophages constitute a key inflammatory cells and IL-17 seems to exert pro-inflammatory actions in the pathogenesis of this condition [65]. Thus, in mouse EAE, systemic blockade of IL-17A results in a delayed onset of disease and also reverses the progression of active EAE; an effect which is associated with a reduced number of CD11b+ macrophages in central nervous system accompanied by the decreased expression of CCL2, CCL17 and CXCL1 chemokines [11].

3.8. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation in the intestinal tract of unknown etiology [66]. The characteristic inflammation in the intestine mucosa is associated with an accumulation of leukocytes and activation of T cells and cells of the monocyte lineage, associated with an impaired local mucosal secretion of various cytokines. In human patients who have moderate or severe ulcerative colitis, as well as in all patients with Crohn’s disease, there is increased IL-17A mRNA expression, as judged from colon biopsies [67,68]. Moreover, IL-17A protein expression is co-localized to T cells and CD68+ monocytes/macrphages [67,68]. These data sets from human patients are compatible with IL-17A operating as a pro-inflammatory cytokine in IBD. However, limited data sets from a mouse model have actually indicated the opposite action of IL-17A. Thus, in the mouse model employing dextran sulfate sodium to induce colitis, the intraperitoneal treatment with an anti-IL-17A antibody actually worsens the disease course [69]. Notably, this increased severity of experimental colitis is associated with increased numbers of CD11b+ monocytes in intestinal mucosa. These data from mice thereby suggest that endogenous IL-17A may play an anti-inflammatory role by contributing to the inhibition of mucosal CD11b+ monocytes [69]. Obviously, the role of IL-17 in IBD is in need of further evaluation.

3.9. Immunoglobulin A Nephropathy

Monocytes are believed to play an important role in the pathogenesis of IgA nephropathy (IgAN), which is form of mesangial proliferative nephritis that is caused by inflammation of internal kidney structures and a local deposition of IgA antibodies in kidneys [70]. Interestingly, PB T cells from IgAN patients spontaneously release more IL-17A than PB T cells from healthy controls [71]. The stimulation of PB CD14+ monocytes from IgAN patients with rhIL-17A results in IL-1β and TNF-α release [71]. Levels of IL-1β and TNF-α are significantly higher in IgAN patients with the nephrotic syndrome than in patients without nephrotic syndrome or in healthy subjects. Up to date IL-17’s effect on cells of the monocyte lineage in IgAN has been evaluated in a very limited number of studies and currently requires further investigation.

3.10. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial inflammation, destruction of
articular cartilage and bone [72]. Although RA is considered to be predominantly a macrophage-mediated disease, the intimate cross-talk between T cells and macrophages is believed to constitute a keystone in the pathogenesis of RA. To date, IL-17A is the only T cell cytokine that is reproducibly detected in substantial amounts in the synovial tissue and fluid from rheumatoid joints of human patients [73-75]. Moreover, IL-17 clearly displays pro-inflammatory properties in RA. It induces: (1) an increase in tissue macrophages and (2) the destruction of tissue by potentiating the osteoclastogenesis from monocytes, induction of “archetype” pro-inflammatory cytokines from cells of the monocyte lineage, as well as eicosanoids and potentially tissue degrading compounds from these cells.

Using an RA model in IL-17R<sup>−/−</sup> knock out mice, it has been shown that endogenous IL-17A is involved in the pathogenic increase of F4/80<sup>+</sup> macrophages in the inflamed synovium [76]. Numerous studies in mice and human have now shown that IL-17 is directly involved in osteoclastogenesis. Osteoclasts are bone-resorbing polykaryons derived from macrophage or myeloid lineage progenitors under the influence of RANKL, a cell-surface molecule from the TNF superfamily, and activated T cells [77,78]. In mice, the osteoclast formation that is induced by rIL-17A is COX-2/PGE<sub>2</sub>-dependent in cultures of bone marrow mononucleated cells and osteoblasts [73]. Of particular interest: the administration of a specific anti-IL-17A antibody inhibits the formation of osteoclasts in co-cultures with media from RA synovial tissue cultures or synovial fluids [73]. Recombinant hIL-17 also induces expression and production of IL-1β and TNF-α from macrophages [7,36]; cytokines that promote tissue degradation in RA [79,80]. The stimulation of freshly prepared human PB monocytes with rhIL-17 causes an up-regulation of monocyte COX-2 expression and production of pro-inflammatory eicosanoids thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and PGE<sub>2</sub> in a concentration-dependent manner [38]. Presumably, the eicosanoid PGE<sub>2</sub> subsequently contributes to the joints’ pain and swelling [81], whereas TXA<sub>2</sub> promotes production of IL-1β and TNF-α by monocytes [82]. In monocyte-derived macrophages, rhIL-17 stimulates an increased mRNA and subsequent protein production of MMP-9 relative to the production of tissue inhibitor of metalloproteinases (TIMP) -1. This excess production of MMP-9 in relation to TIMP-1 is believed to contribute to cartilage degradation and joint destruction [39,83]. Thus, extensive data sets from RA studies implicate that IL-17 plays an important role in the pathogenesis of this disease. Of particular importance is the fact that the majority of IL-17<sup>+</sup> cells express large quantities of IL-17A. Taken together, these data indicate that in LCH, the main cellular source of IL-17A is not the T cell population, but the DC subpopulation. In vitro studies have shown that administration of rhIL-17 induces the fusion of DC and the formation of giant multinucleated cells, and that IFNγ and TNF-α increase this IL-17A-induced DC fusion. Importantly, the IL-17A-dependent fusion activity in the serum from LCH patents does parallel the disease activity. These giant cells are loaded with major tissue-destructive enzymes; tartrate resistant acidic phosphatase and MMP-9 and 12. Indeed, this single study in humans points out the potential importance of IL-17 in tissue degradation and suggests possibility of autocrine regulation of IL-17 effects on cells of the monocyte lineage [20].

### 3.12. Asthma

It is known that airway inflammation in asthma is associated with a local increase in macrophages; a cell population that in many asthmatic patients represent the dominating population of inflammatory cells in the airways [85,86]. Recent studies have shown that cells expressing IL-17A and IL-17E are present in airways of patients with asthma [17,21,87]. The number of IL-17A-positive cells is increased in the airway lumen and in the blood of patients with asthma, when compared with healthy controls [17,21,88] and is associated with airway hyperreactivity [89]. Furthermore, allergen challenge induces gene expression of another IL-17 family cytokine, IL-17F, in asthmatic airways [90]. In a mouse model of OVA-induced airway inflammation, the blockade of endogenous IL-17A results in a decreased total number of alveolar macrophages and MMP-9<sup>+</sup> alveolar macrophages [21,91]. Notably, recombinant mouse (m) IL-17A prolongs the survival of the airway macrophages in a concentration-dependent manner in vitro, which is accompanied with a decreased expression of Fas on macrophages in vivo. Interestingly, airway macrophages from allergen-challenged mice are more susceptible to stimulation with exogenous rmIL-17 than are macrophages from vehicle-exposed mice, with reference to survival in vitro. Additionally, rmIL-17 directly induces the migration of blood monocytes from allergen-challenged mice in vitro. Overall, the referred study on mice shows that IL-17A is involved in allergen-induced accumulation of macrophages in inflamed airways via its direct stimulatory effect on cell chemotaxis and survival [91]. In addition, mice with the induced over-expression of IL-17A or IL-17E protein in the airways develop a local inflammation that is associated with increased numbers of macrophages and CD11c<sup>+</sup> DC [11,92]. In this particular experimental setting, the increased number of macrophages is associated with an increased expression of several chemokines, including CCL7, CCL22, CCL20, CCL11, CX3CL1 in the lung tissue [11].

### SUMMARY

As discussed in the current review, IL-17 can do more than merely promote the accumulation of neutrophils in various organs. In fact, IL-17 is a true pleiotropic cytokine that can behave either as a pro- or an anti-inflammatory sig-
nal, depending upon the specific pathologic setting. Thus, in infection IL-17 via its effects on macrophages may stimulate antimicrobial activity and thereby contribute to host defense. In contrast, in allograft rejection, autoimmune myocarditis, autoimmune encephalomyelitis, IgA nephropathy, rheumatoid arthritis, Langerhans cell histiocytosis and asthma, IL-17 effects on various cells of the monocyte lineage are associated with increased disease severity, suggesting a causative role in pathogenesis. In IBD, performed studies have suggested that IL-17 can act both as a pro- and an anti-inflammatory mediator within the same disease setting, thereby pointing out that additional factors, possibly related to the microenvironment surrounding target cells, are of key importance [67-69]. Tentatively, current experimental and clinical evidence support that IL-17 is involved into the production [42,43], maturation [8,20,73,93], recruitment [9,11,58,69,76,91,92] and functional behavior [7,20,39,48,49,61,71,91] of cells from the monocyte lineage in health and disease. The causal relationship between IL-17 and cells of the monocyte lineage is most extensively studied in RA: these studies suggest a crucial importance of IL-17 for the biology of cells of the monocyte lineage, cells that are believed to have a fundamental role in the development and progression of RA. Overall, the emerging understanding of IL-17’s potential clinical importance for cells of the monocyte lineage in humans is prompting further investigation.

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REFERENCES


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