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Review article

IL-17 and colorectal cancer: From carcinogenesis to treatment

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ABSTRACT

Colorectal cancer (CRC) is one of the most common types of cancer in the world. Several factors contribute to the development of this cancer. Tumor formation in colon triggers immune responses such as immune cells proliferation, phenotype alteration, cytokine synthesis and release, which lead to IL-17 producing T cells, the differentiated CD4+ T cells i.e. T helper 17. IL-17 is a pro-inflammatory cytokine, which its level is up regulated in serum and tissues of CRC patients. Several studies have shown that IL-17 has an important role in metastasis and prognosis of CRC. The aim of this review is to summarize the role of this cytokine in tumorigenesis, angiogenesis and metastasis of CRC and discuss its value in diagnosis, prognosis and treatment of CRC.

1. Introduction

Colorectal cancer (CRC) is the second most common type of cancer in women and the third most common type of cancer in men [1]. It is expected to occure 50,260 deaths in USA due to CRC in 2017 [2]. There are several factors that can increase the risk of CRC development such as old age, inflammatory bowel diseases, type 2 diabetes mellitus, Ashkenazi Jewish heritage and African-American ethnicity. Some factors that are related to the lifestyle, such as obesity, diet, heavy alcohol consumption, smoking and lack of exercise have also been attributed to the increased risk of CRC [3,4]. In addition, CRC has an early onset in patients with a mutated adenomatous polyposis coli (APC) gene which is responsible for causing familial adenomatous polyposis (FAP). Additionally, 5–10% of CRC cases are associated with hereditary disorders like lynch syndrome [5,6].

After tumor formation in colon, immune system reacts against neoplastic cells. Immune responses include immune cells proliferation, phenotype alteration, synthesis and release of cytokine [7] such as interleukin-17 (IL-17). IL-17 is a pro-inflammatory cytokine, which is associated with cancer progression [8]. The main source of IL-17 is a subpopulation from CD4+ T cells known as T-helper17 (Th17) cells. [9]. Tumor infiltrating Th17 cells were found in many types of cancers [10,11]. Several agents are required for differentiation and stabilization of Th17 cells such as: transforming growth factor beta (TGF-β), interleukin-6 (IL-6), IL-21, IL-23 and IL-1b. Also, retinoic orphan receptor-γ (RORγ) and signal transducer and activator of transcription 3 (STAT3) are the transcription factors responsible for Th17 differentiation and stabilization (Fig. 1) [7,9,12–16]. Although, the name of Th17 cells comes from their ability to produce IL-17, they also release other cytokines such as IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [17]. It should be noted that IL-17 is also produced by other sources such as natural killer cells (NK), CD8+ T cells, neutrophils, eosinophils, macrophages, dendritic cells and gamma delta T cells (γδT) (Fig. 1) [16,18]. Regulatory T (Treg) cells, generally known as immune suppressors, also produce IL-17. In steady states, the production of IL-17 from Treg cells is inhibited by binding of transcription factor forkhead box P3 (Foxp3) to RORγ [19].

IL-17 family consists of 6 cytokines with IL-17A as the prototype and five additional members, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25) and IL-17F. IL-17A and IL-17F have the highest homology and IL-17E has the least [20]. Among different classes, IL-17A, E and F are more studied. IL-17A and F induce chemokines for neutrophil recruitment and IL-17E induce production of Th2 cytokines and recruit Eosinophils [21]. Published data have shown that IL-17 level is increased in the sera and tumor tissues of CRC patients [7,22–27]. In addition, several studies have demonstrated that IL-17 has a significant role in

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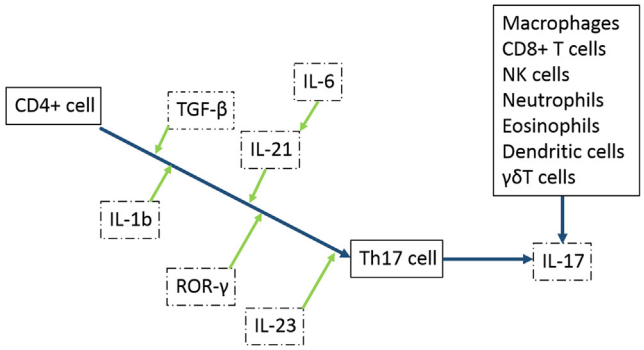

Fig. 1. Schematic role of different cytokines in Th17 differentiation from CD4+ T-cells, and subsequent IL-17 production. CD4+ T cells differentiate into Th17 cells by using several agents including: TGF-β, IL-6, IL-21, IL-23, IL-1b and RORγ. Th17 cells secrete IL-17. Additionally, this cytokine can be produced by several other cells such as macrophages, CD8+ T cells, NK cells, neutrophils and eosinophils.

metastasis and prognosis of CRC [25,28–30]. In this study, we willreview the role of IL-17 in tumorigenesis, angiogenesis, and metastasis of CRC, and discuss the importance of this cytokine in diagnosis, prognosis and treatment of CRC.

2. The role of IL-17 in tumorigenesis of colorectal cancer

CRC progression is a process that involves interactions between the tumor and the host cellular immunity in the tumor microenvironment. Neoplastic cells secrete pro-inflammatory mediators and immune cells produce cytokines which all lead to tumor development [31]. Studies have shown that the number of Th-17 cells are significantly higher in CRC tissues [25,26,32]. Th17 cells induce immune suppressive mediators such as TGF-β, CXCR3, CC chemokine receptor 6 (CCR6) and IL-6 [33]. They also suppress CD8+ T cells which have anti-tumor activity [34]. Moreover, it has been shown that the number of IFN-γ producing CD8+ T cells is increased in the IL-17 deficient mice [35].

IL-17 is produced by Th17 cells and it is an important cytokine in various immune responses such as type2 immune response. In pro-inflammatory responses, IL-17 plays an important role in activation and recruitment of neutrophils. Neutrophils are the main sources of cytokines related to Th2-type immune response that induce negative feedback, suppress neutrophilia, decrease tissue destruction, and also induce IL-17 production [36].

Published data demonstrated that the level of IL-17 was significantly higher in CRC tissues [7,22,23,25–27,37]. Cui et al. have shown that the up-regulation of IL-17 begins from adenoma stage and its level is higher at the cancer stage but it is not associated with TNM parameters of the tumor [7]. Therefore, IL-17 is involved in CRC tumorigenesis through several pathways:

2.1. IL-17 and myeloid-derived suppressor cells

IL-17 can promote CRC tumorigenesis by promoting the production of myeloid-derived suppressor cells (MDSCs). These cells are a heterogeneous population of cells consisting of immature myeloid cells and myeloid progenitor cells [38]. IL-17 stimulates IL-6 secretion from stromal and tumor cells. IL-6 activates STAT3 pathway [39,40]. This pathway regulates the expression of some inflammatory factors such as CXC chemokine ligand-1 (CXCL1), Cyclooxygenase 2 (Cox2), S100A8/9 and IL-1b, which can shift the steady-state myelopoiesis from immature myeloid cells towards pro-carcinogenic myeloid cells such as MDSCs [41]. Thiele Orberg et al. showed that IL-17 is also important for recruitment of MDSCs [41]. This cytokine up-regulates the immunosuppressive function of MDSCs as well [35,42]. MDSCs can inhibit antigen-specific and non-specific T cell activation. These cells use several mechanisms to inhibit anti-tumor immunity such as increasing the level of nitric oxide (NO), reactive oxygen species (ROS) and arginase1 (Arg1) (Fig. 2) [43–45]. Zhang et al. showed that selective decrease in MDSCs can slow down colitis associated cancer process [42].

2.2. IL-17 and tumor necrotic factor α (TNFα)

Tumor infiltrating macrophages produce TNFα that can stimulate transcription of nuclear factor Kappa Beta (NF-kB) and IL-17 genes. NF-kB induces glycolysis and prepares the energy for tumor cells. TNFα

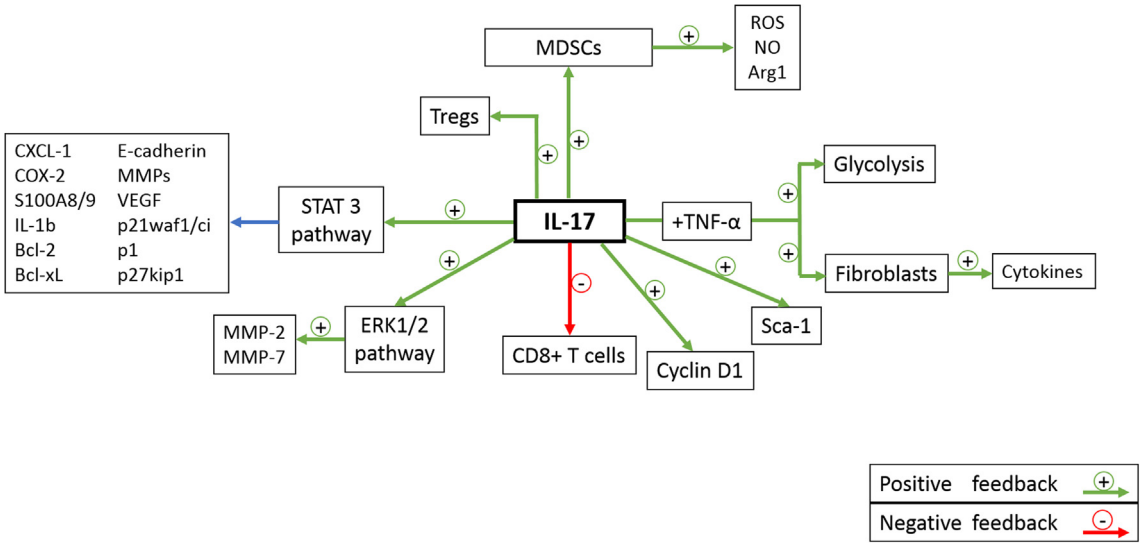

Fig. 2. Schematic role of IL-17 in tumorigenesis. IL-17 decreases the number of CD8+ T cells and increases the activity of Tregs. In addition, IL-17 can promote the function of MDSCs. These cells suppress anti-tumor immunity by using several mechanisms such as increasing the level of ROS, NO and Arg1. TNFα, which is produced by tumor infiltrating macrophages and IL-17 have a synergistic effect on promoting glycolysis. Additionally, they can increase survival and proliferation of fibroblastic cells that can produce cytokines with positive effect on tumor cell proliferation. IL-17 up-regulates the expression of Sca-1 marker and it can also control cyclin D1expression. In addition, ERK1/2 pathway is increased by IL-17, which leads to increased MMP-2 and MMP-7 expression. IL-17 also increases activation of STAT3 pathway and this pathway enhances the expression of some genes including CXCL-1, COX-2, S100A8/9, IL-1b, Bcl-2, Bcl-xL, E-cadherin, MMPs, VEGF, p21waf1/cip1, p27kip1.

and IL-17 also resemble synergistic effect on stimulation of HT-29 cells. HT-29 cells are human colorectal adenocarcinoma cell line. These cells produce hypoxia-inducible factor 1 alpha (HIF-1a), which is a main regulator of genes that encode the components of glycolysis and c-myc oncogene. In addition, TNFα + IL-17 stimulate HT-29 cells to produce factors that can increase proliferation and survival of fibroblastic cells. Fibroblastic cells secrete factors that can enhance tumor cells proliferation. Therefore, IL-17 + TNFα might promote metabolism and growth of CRC tumor cells by growth factor production and glycolysis (Fig. 2) [46].

2.3. IL-23/IL-17 pathway

Several studies represented that IL-23/IL-17 pathway has a critical role in pathogenesis of CRC [26,47]. Grivennikov et al. showed that microbial products stimulate tumor-associated myeloid cells to produce IL-23 in intestine. IL-23 promotes the production of IL-17 and stimulates STAT3 pathway [26]. IL-23/IL-17 signaling pathway reduces the number of CD8+ T cells (Fig. 2) [34] and increases the immunosuppressive activity of Treg cells (Fig. 2) [48], resulting in tumor growth and progression. In addition, STAT3 pathway plays a crucial role in CRC growth, invasion and survival by regulating the expression of genes such as: Bcl-2, which is an anti-apoptotic gene, E-cadherin, matrix metalloproteinases (MMPs), VEGF, p21waf1/cip1 and p27kip1(Fig. 2) [49].

2.4. The effect of IL-17 on ERK1/2 signaling pathway and cyclin D1

Xie et al. found that IL-17 activates extracellular receptor kinase (ERK)1/2 signaling pathway in HT-29 cells. ERK1/2 pathway can increase IL-17 downstream genes such as MMP-9, MMP-7 and MMP-2 (Fig. 2). MMP-7 and MMP-2 assist in tumorigenesis and can induce invasion and metastasis of tumor. Xie et al. also showed that IL-17 increases IL-6 expression which leads to increased levels of the anti-apoptotic proteins such as Bcl-2 and Bcl-xL, and the up-regulated level of Bcl-2 in colon adenomas and adenocarcinomas. They also demonstrated that cyclin D1, which is contributed to increased cell proliferation, is controlled by IL-17 (Fig. 2) [3]. In addition, another study by Hyun et al. showed that IL-17 knockout mice demonstrated decreased expression of cyclin D1 in colitis associated cancer [50].

2.5. The effect of IL-17A on stem cell antigen

Do Thi et al. demonstrated that CRC cells, which expressed IL-17 had higher expression of Sca-1 [12]. Sca-1 is a stem cell marker on normal tissues. Some studies showed that Sca-1 plays a role in tumorigenicity of mammary and prostate cancers by suppressing TGF-β, which is an anti-inflammatory cytokine [51–53]. Therefore, IL-17 can increase the level of Sca-1 which leads to tumorigenesis in colon (Fig. 2).

2.6. Role of different members of IL-17 family in tumorigenesis

Different family members of IL-17 exert different roles in tumorigenesis. While IL-17A has a pro-tumorigenic effect on CRC, IL-17F protects against colitis-associated colon cancer [54] and CRC. It has been shown that the level of IL-17F is decreased in CRC patients [24,55,56]. IL-17B is up-regulated in patients with CRC and it can stimulate colon sub-epithelial myofibroblasts to secrete IL-6 and IL-8. Therefore, IL-17B can promote inflammation, which could lead to CRC. The expression of IL-17C is different depending on the grade of cancer and it tends to decline in advanced cancer. There was no difference between the expression of IL-17E in CRC and normal tissue [55]. However, Benatar et al. showed that IL-17E can be used as an anti-cancer agent in CRC [57].

2.7. Anti-tumor function of IL-17

Some studies have reported the anti-tumor function of IL-17. Lin et al. demonstrated that IL-17 expression is associated with early stage CRC and better prognosis in patients with CRC. In addition, they showed that the number of tumor infiltrating neutrophils is correlated with IL-17 expression in CRC. Tumor infiltrating neutrophils release myeloperoxidase and hydroperoxide which have anti-tumor activity [37]. However, another study represented that IL-17 expression is not directly correlated with neutrophil recruitment but it can induce the expression of some pro-inflammatory mediators such as CXC chemokines release from stromal cells, which results in recruitment of neutrophils [58]. However, it should be considered that researchers used various markers to identify neutrophils and these different results might be contributed to the different subgroups of neutrophils [37]. A study by Kryczek et al. showed that the subcutaneous inoculation of murine colon cancer cell line named MC38 into IL-17 deficient mice leads to faster tumor growth and more foci of lung metastasis compared to wild-type mice. Additionally, IFN-γ+ immune cells including tumor specific NK cells, CD4+ T cells and CD8+ T cells were reduced in tumor infiltrating lymph nodes in IL-17 deficient mice [59]. Another study demonstrated that IL-17 plays an important role in promoting recruitment of NK cells by activating the production of MCP-1 chemokine from tumor endothelial cells [60]. In addition, Lu et al. represented that IL-17 can stimulate tumor cells to produce chemokine (C-C motif) ligand 20 (CCL20) resulting in recruitment of DCs [61]. As a result, these studies suggest that IL-17 can induce anti-tumor immunity through recruitment of lymphocytes, NK cells and DCs into the tumor site. Also, IL-17 can increase NK cell activity by stimulating the expression of adhesion molecules, which can facilitate the binding of tumor cells and NK cells [62]. This cytokine also enhances the cytotoxic activity of NK cell either by enhancing the expression of activation receptors such as NKG2D, NKp44, NTB-A and NKp46 or by increasing the expression of cytotoxic molecules such as perforin, TNFα, INF-c and granzyme B [61]. In addition, it has been shown that IL-17 can stimulate the activity of tumor specific T cells and results in suppression of tumor growth. Different mechanisms have been proposed for activation of tumor specific T cells by IL-17. For instance, Benchetrit et al. showed that IL-17 induces the expression of IL-6 [63]. IL-6 has anti-tumor activity and can stimulate tumor specific T cells [64]. Additionally, IL-17 can stimulate macrophages to secrete IL-12 [65], which can activate the production and activity of cytotoxic T lymphocytes (CTLs) [66,67]. Yang et al. also showed that IL-17 has anti-tumor effects on CRC. They found that IL-17 gene transfection decreases the expression of IL-10 and IL-13 factors and these factors can increase the progression of CRC. They also showed that IL-17 increases the expression of interferon gamma (IFN-γ), which has anti-tumor activities in the tumor tissue. Moreover, they showed that IL-17 increases the count of T lymphocytes infiltrated in tumor tissue [18].

3. The role of IL-17 in angiogenesis of colorectal cancer

It has been shown that angiogenesis that is mostly activated by vascular endothelial growth factor (VEGF), plays an important role in tumor growth and metastasis [68]. Published data showed that IL-17, which is a pro-inflammatory cytokine, can directly affect the angiogenesis of CRC by binding to the IL-17 receptors (IL-17R) on the endothelial cells and stimulating these cells to produce VEGF, which could activate cancer cells indirectly to generate angiogenic factors. In addition, a study by Liu et al. showed strong expression of IL-17R on CRC cells. They did PCR-array and real time PCR and concluded that VEGF is the most fundamental angiogenic mediator, which is induced by IL-17 in CRC [25]. In another study, Wagsater et al. showed that VEGF expression of tumor cells was significantly higher than normal in CRC cells [69]. Numasaki et al. studied the mice models for fibrosarcoma and colon adenocarcinoma. They found higher vascular density in

tumors transduced with IL-17. In their work, IL-17 did not directly stimulate endothelial cell's growth, but it induced migration of endothelial cell and cord formation of vascular endothelial cells [70]. By considering the promoting effect of IL-17 on VEGF production, Chung et al. suggested that IL-17 is responsible for inducing resistance to anti-tumor and anti-angiogenic effects of the drugs that can block VEGF [71]. However, several articles showed that some members of IL-17 family such as IL-17F can inhibit angiogenesis. A study by Tong et al. showed that the level of VEGF is up-regulated in the colon tissues of IL-17F deficient mice with cancer. This result represent the protective role of IL-17F in colon cancer through inhibiting tumor angiogenesis [56].

4. The effect of IL-17 on metastasis of CRC

Metastasis is the major cause of death in patients with CRC [22] and 50% of patients, whose primary tumor was surgically removed, suffered relapse and finally died due to metastatic disease [72]. Published data have shown that IL-17 can induce metastasis by several mechanisms in CRC. IL-17 stimulates p38 and ERK phosphorylation, which results in NF-kB p65 phosphorylation. NF-kB is a transcription factor that has a binding site on promoter of CCR6 gene in CRC cells. Therefore, by this pathway, IL-17 can stimulate CCR6 expression, which plays a significant role in migration and metastasis of CRC cells (Fig. 3) [29]. In addition, a study by Dellacasagrande et al. showed that CRC liver metastasis tissues had higher level of CCR6 compared to surrounding tissues [73]. A study by Wang et al. represented that IL-17 induces the expression of MMP-9 and MMP-13 in CRC cells, which are significant for tumor metastasis (Fig. 3) [30]. This result is consistent with the result of a study by Tseng et al., in which IL-17 increased the expression of MMP-9 [22]. Additionally, IL-17 stimulates production of prostaglandin E2 (PGE2), which is involved in the migration of CRC cells (Fig. 3) [74]. As mentioned before, IL-17 can also promote the angiogenesis by increasing the production of VEGF (Fig. 3) [75].It has been shown that angiogenesis plays a significant role in tumor metastasis as well [76].

5. IL-17 as a diagnostic marker

Early detection of CRC plays an important role in reducing mortality in patients. Evidence suggest that IL-17 can act as a diagnostic marker in several types of cancer such as esophageal carcinoma [77]. Moreover, increased level of IL-17 has been detected in the sera of CRC patients and therefore it can be a favorable diagnostic marker in patients with CRC [78].

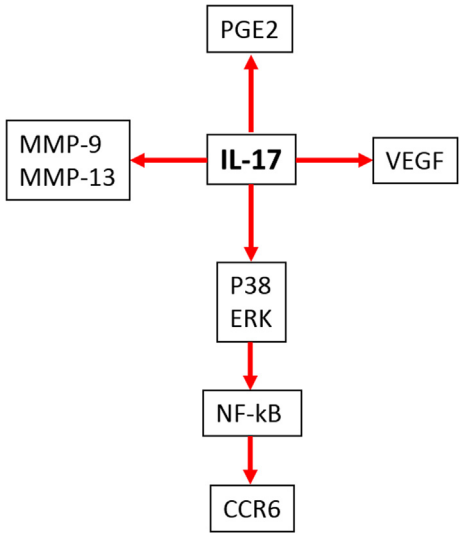

Fig. 3. Schematic role of IL-17 on metastasis. IL-17 activates P38 and ERK phosphorylation which leads to NF-kB p65 phosphorylation. NF-kB induces CCR6 gene expression which plays an important role in metastasis of CRC cells. In addition, IL-17 can stimulate the expression of some tumor invasion factors such as MMP-9 and MMP-13. The production of PGE2 and VEGF is also activated by IL-17.

6. IL-17 can act as a prognostic marker in CRC patients

Higher expression of IL-17 in tissue and serum of patients with CRC suggests that this cytokine could be used as a prognostic marker in CRC [79]. IL-17 promote angiogenesis [25] and PGE2 production, which both lead to the better survival of CRC cells [74]. A study by Schetter et al. reported increased level of IL-17 is associated with poor prognosis of CRC [80]. Additionally, Liu et al. showed that 5 year survival of 26 patients with lower IL-17 level was 72.41% and it was 38.08% in 26 patients with higher IL-17 level [25]. Hyun et al. demonstrated that the incidence of colitis associated colon cancer is significantly decreased in IL-17 deficient mice [50]. However, a study by Lin et al. showed that IL-17 expression is associated with good histological differentiation and early Duke's stage. Also, Kaplan-Meier analysis represented that survival rates were longer in patients with higher level of IL-17 and therefore, they suggested that elevated level of IL-17 contributes to good prognosis in patients with CRC and it might be a protective agent in CRC progression. These results are different from the results of Liu's study. This is perhaps due to the fact that Lin et al. included patients with different stages of the CRC but Liu et al. only included patients with stage III CRC [37].

7. The role of IL-17 in the treatment of CRC

Surgical resection of tumor and the lymph nodes near the tumor is a preferable therapeutic strategy for patients with early stage CRC and surgery combined with adjuvant therapy is used for patients with advanced stages of CRC [81]. Nevertheless, considering all aforementioned studies, there is no surprise that several studies investigated IL-17 as a new target for treatment and prevention of CRC [3,22,23,82]. Various therapeutic approaches can be useful in the treatment of CRC patients. Monoclonal antibodies that target cytokines, such as IL-23, IL-17 and IL-17R [3,23,82], small molecules such as retinoic acid receptor-related orphan nuclear receptor RORγt antagonists that can inhibit Th17 differentiation, molecules that can restore barrier function, which leads to inhibition of IL-23 production by tumor associated macrophages [82–85] and molecules that can reduce IL-17 production or can block the downstream of IL-17 [82] are among the options for treatment of CRC. It should be noticed that none of these drugs could induce anti-tumor effect by its own and these drugs should be used in combination with chemotherapeutic drugs such as anti-angiogenic agents, oxaliplatin, 5-fluorouracil and anti-EGF receptor antibodies [86]. Benatar et al. have also shown that IL-17E has anti-tumor effect against colon adenocarcinoma and it could be used alone or in combination with other drugs [57]. In addition, monoclonal antibodies against IL-17 are now available. Secukinumab and Ixekizumab bind to IL-17A and are mostly used in patients with psoriasis, psoriatic arthritis and Ankylosing Spondylitis [87,88]. In a study by Esfahani et al, a patient treated with Pembrolizumab for metastatic CRC, experienced Psoriasis flare-up. Secukinumab administration controlled Psoriasis, however, biochemical response of carcinoemryonic antigen was lost and disease progression was observed in serial CT scans [87]. In addition, there are reports of potential benefits of targeting IL17-A in different cancer types, as esophageal squamous cell carcinoma [89] and multiple myeloma [90].

8. Conclusion

In conclusion, IL-17 can promote CRC tumorigenesis by several pathways such as stimulating the production and recruitment of MDSCs. IL-17 can also up-regulate the immunosuppressive function of

MDSCs. Glycolysis and growth factors that can provide nutrition and growth signals for tumor cells can be increased by IL-17. IL-17 enhances the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-x. This cytokine can also increase immunosuppressive mediators such as TGF-β, IL-6, CCR6 and CXCR3. IL-17 suppresses CD8+ T cells and increases the immunosuppressive activity of Treg cells. On the other hand, IL-17 exerts anti-tumor activity by decreasing the level of IL-10 and IL-13 and enhancing the level of IL-6, IL-12 and IFN-γ. Moreover, it can induce the activity of NK cells and tumor specific T cells. The number of tumor infiltrating neutrophils can be increased by IL-17. In addition, it has been proposed that IL-17 induce anti-tumor immunity through recruitment of lymphocytes, NK cells and DCs into the tumor microenvironment. Therefore, more research is required to determine the exact role of this cytokine in CRC tumorigenesis.

Angiogenesis plays an important role in progression and metastasis of CRC and IL-17 is involved in these processes as well. It can induce angiogenesis by stimulating the production of VEGF, MMP-9, MMP-13, CCR6 and PGE2. These mediators can promote metastasis in CRC. Therefore, IL-17 can contribute to metastasis of CRC by inducing angiogenesis. Published data showed that IL-17 is associated with poor prognosis of CRC patients due to increased angiogenesis. In contrast, there are other studies, which showed that IL-17 is a protective cytokine against CRC. Therefore, the role of IL-17 in prognosis of CRC patients is still uncovered and more studies are needed.

Due to the roles of IL-17 in tumorigenesis, angiogenesis, metastasis, diagnosis and prognosis of CRC, this cytokine has been a new target in treatment of CRC patients. Various therapeutics have been developed for treatment of CRC. The therapeutics include monoclonal antibodies that target IL-17 or IL-17R, molecules that can inhibit Th17 differentiation or inhibit the stimulation of IL-23 or can reduce IL-17 production.

Declaration of interests

The authors declared that there is no conflict of interest.

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