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Revisiting the Roles of IL-17 in Colorectal Cancer

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Abstract: ***Colorectal cancer is an important contributor to cancer-associated mortality and morbidity in developed countries. Inflammation is an important factor that leads to the development of colorectal cancer and several inflammatory cytokines are associated with the development of this type of tumor. The interleukin-17 (IL-17), a pleiotropic proinflammatory cytokine, can promote cancer-induced inflammation by recruiting monocytes and neutrophils to the site of inflammation. In this review, we are dedicated to summarizing and revisiting the main aspects related to colorectal cancer and the role of IL-17 in this scenario.***

Keywords: colorectal cancer, inflammation, IL-17

1. Introduction

Colorectal cancer is a type of tumor that despite several treatment alternatives still contributes to mortality and morbidity [1]. Several inflammatory cytokines such as IL-17 have been shown to promote colorectal cancer progression in the context of chronic inflammation [2, 3].

The cytokine IL-17 comes from Th17 cells that arise from the differentiation of $CD4^+$T cells. Depending on the signal that $CD4^+$T cells receive, they also can differentiate into Th1, Th2, and Treg. Signals that drive Th17 differentiation include TGFβ, IL-6, IL-1β, or IL-21 [4]. These cytokines stimulate the expression of lineage-defining transcription factor ROR-related orphan receptor gamma t (RORγt) and the secretion of IL-21, GM-CSF, and IL-22, in addition to IL-17 which encompasses six homologous proteins (from IL-17A to IL-17F) [5, 6].

The IL-17 is upregulated in serum and tissues of CRC patients. The IL-17 upregulation begins from the adenoma stage and IL-17 can suppress $TCD8^+$ cells contributing to a worsening prognostic of CCR [7]. Several studies investigated IL-17 as a new target for the treatment and prevention of CRC and show that monoclonal antibodies that target cytokines, such as IL-23, IL-17, IL-17R, and receptor RORγt antagonists can inhibit Th17 differentiation or reduce IL-17 production, may be important tools to the treatment of CCR and for the understanding of the IL-17 involvement in the physiopathology of this cancer, which can result in novel purposes of treatment.

Pathophysiology of colorectal cancer

Starting the Neoplastic Process

Cellular mutations can lead to the occurrence of a colorectal neoplasm, induced by external exposure, such as carcinogens-tobacco, alcohol, nitrates-or due to genetic alterations [8].

The epithelial cells that enrobe the gastrointestinal tract, mostly the colon and rectum, have a high cell turnover, which occurs in the intestinal crypt. These structures are composed of enterocytes, enteroendocrine cells, goblet cells, and, in the lower portion, stem cells [9]. The cell replication process begins in the basal portion of the crypts, ascending to the surface when they become differentiated. The cells that reach the luminal portion of the crypt carry out an apoptosis process and detach without replicating or differentiating [9].

Cells carrying genetic mutations do not execute the apoptosis process properly when they reach the crypt surface and continue cellular self-replication. The occurrence of this alteration is a precancerous sign, highlighting a focus of cellular abnormality, or in other terms, a focus of an aberrant crypt (ACF). This pattern of cell replication abnormality (CFA) was associated with a risk for the possible development of malignant colorectal cancer. Therefore, it was identified in patients with Familial Adenomatous Polyposis (FAP), chronic inflammatory bowel diseases, advanced age, and patients who had previously undergone a polypectomy [10].

Cellular changes can pre-determine the formation of polyps in the colon. However, the term “polyp” should not be used solely to diagnose the existence of a colorectal neoplasm. A polyp is a clinical description of a mass that extends beyond the mucosal surface and can be defined as well-delimited and circumscribed nodules in a crypt region with abnormal cell division [11].

The polyps can be differentiated into hyperplastic, inflammatory, adenomatous, and malignant. The first ones have a lower malignancy potential than the adenomatous [11, 12]. Furthermore, most polyps are benign with asymptomatic lesions and a small portion of them can progress to malignancy, developing in this way a colorectal

carcinoma [11, 12]. Otherwise, adenomas are nodules demarcated by tumor epithelial cells, which have different degrees of alterations in their cytoplasmic architecture. The technical term to classify these modifications is called "dysplasia". Thus, adenomas are classified considering the most advanced degree of cellular dysplasia, being specified as mild, moderate, or severe [11, 12].

The Evolution of the Disease

As far as Colorectal neoplasia is concerned, in its evolutionary course, it can start in a benign way and progress to a stage of malignancy. This succession may occur due to the high number of genetic and molecular alterations found in CRC that may contribute to this progression. The existence of various stages of cellular atypia in the colon supports the evidence for an evolutionary sequence from adenoma, a benign state, to carcinoma, a stage of malignancy. Almost all colorectal carcinomas are evolutions of adenomas that progressed to infiltrative lesions with high cell differentiation [12].

Several molecular-level abnormalities have been identified in colorectal adenomas, including mutations in oncogenes, inactivation of tumor suppressor genes-APC gene, p53, and DCC, the presence of mutated genes such as MLH1 and MSH2, and disturbances in DNA methylation [13].

IL-17

IL-17 Cytokines and Functions

IL-17 is a cytokine family composed of at least 6 members: IL-17A, B, C, D, E (also called IL-25), and F [14, 15]. IL-17 cytokines participate in both acute and chronic inflammation as they stimulate the production of proinflammatory cytokines and chemokines by other immune cells and promote more rapid recruitment of neutrophils and monocytes to the site of inflammation [16]. The cytokines also play an important role in barrier integrity through the maintenance of tight junctions in the intestinal mucosa and, in case of tissue damage, through the stimulation of tissue regeneration to restore barrier function [17].

The overabundance and chronic activity of the IL-17 are associated with different pathological conditions, especially inflammatory and auto-immune diseases, as well as cancer [18]. In pathological settings, the cytokines of the IL-17 family induce the mitogenic effect in tissue progenitor cells and reprogram cellular metabolism, which can drive tumorigenesis and cancer progression. In accordance with studies on other cancers, growing evidence has shown that IL-17 can also promote tumor progression in CRC [16]. In the intestinal tumor-bearing model, the tumor size is significantly reduced in IL-17 gene-knockout mice compared with wide-type (WT) mice, and anti-IL-17A monoclonal antibody treatment results in decreased tumor size in the WT mice [19].

Cytokine Expression and Secretion

Although all from the same family, the IL-17 cytokines have different cellular sources. IL-17A and F cytokines are produced by Th17 cells, $CD8^+$ cytotoxic T (Tc) cells, and innate tissue-resident cells that are activated on injuries [20]. It has also been suggested that IL-17A is expressed by myeloid cells, such as macrophages, mast cells, and neutrophils [21-23]. IL-17E, also known as IL-25, has both hematopoietic and nonhematopoietic sources [24].

IL-17C is expressed by epithelial cells after stimulation by TLR2, TLR5, and proinflammatory cytokines and it is not expressed by hematopoietic cells. Some examples of epithelial cells that express IL-17C are keratinocytes, colonic epithelial cells, respiratory epithelial cells, and resident kidney cells [25].

IL-17B and D are expressed in the intestinal epithelium, chondrocytes, and neurons. Some other sources for IL-17B are neutrophils and naive, memory, and germinal center B cells [27]. In regards to its expression in immune cells, IL-17D was seen in $CD19^+$ B cells and in resting $CD4^+$ T cells [27].

Receptors and Signaling

The family of IL-17 receptors has 5 members (IL-17RA-RE) and they all share sequence homology [14]. The cytokines of the IL-17 family all signal through a heterodimeric receptor formed by IL-17RA and another subunit, which determines the cytokine that will bind to the receptor [27].

The IL-17A cytokine signals through a heterodimeric receptor complex (formed by IL-17RA and IL-17RC). The receptor IL-17RA is uniformly expressed across tissues, but IL-17RC has a more restricted expression, which limits signaling mostly to non-hematopoietic epithelial and mesenchymal cells. It is proposed that when a ligand binds to the first receptor subunit the affinity and specificity of the second binding event are altered, promoting, therefore, the formation of a heterodimeric receptor complex [28]. Since IL-17F shares great (56%) sequence homology with IL-17A, it also signals through the same receptor complex (although with lower affinity). IL-17B binds to IL-17RB with high affinity [28]. IL-17C signals through the IL-17RE receptor [28]. IL-17E signals through a receptor complex formed by IL-17RB, which is also known as IL-25R, and IL-17RA. The receptor for IL-17D remains unknown [27, 28].

Cytokines from the IL-17 family signal through their correspondent receptors and activate pathways to promote the expression of chemokines, antimicrobial peptides, and other cytokines. This process depends on a region in the cytoplasmic region of all IL-17 receptors: the "SEFIR" or "SEF/IL-17R" [29]. SEFIR is a platform that promotes the interactions between IL-17 receptors and Act1, a mediator that will activate the signaling cascades of all IL-17 cytokines [29]. In the colonic epithelium, Act1 can bind to the growth factor receptor-bound protein 2 (GRB2) and suppress the extracellular signal-regulated kinase 1/2 (ERK1/2), which allows for tissue repair in cases of inflammation.

It is important to highlight that the mechanisms of IL-17 signaling are not yet fully known and there are different IL-17 signaling pathways induced by IL-17 [30].

IL-17 and the Gastrointestinal Tract

The IL-17 cytokines can play both protective and exacerbating roles in intestinal inflammation [31]. It has

been shown that IL-17A has a protective role by signaling through Act1 on epithelial cells. In the absence of Act1, however, this protective role can be abrogated and inflammation is enhanced [32]. One example of an exacerbating role is the upregulation of IL-17A, F, and Th17 cells in the intestinal mucosa of patients with Crohn's disease and ulcerative colitis [33]. In regards to the protective role, IL-17A, for example, was shown to inhibit Th1 polarization for IFN-γ dependent inflammation in cases of T-cell mediated colitis [34].

In the gastrointestinal tract, IL-17C assists innate host defense and also regulates intestinal inflammation through the promotion of cytokines and anti-microbial peptides [35]. In the normal gastrointestinal tract, the intestinal epithelial cells are joined together by tight junctions, which stop bacterial invasion [36]. In regards to the integrity of this barrier, IL-17C directly contributes to the expression of occludin, a tight junction molecule in colonic epithelium, while IL-17A is necessary for the regulation of this molecule during any epithelial injury [14]. Therefore, both cytokines are of great importance to the maintenance of the function of the intestinal barrier [14].

IL-17 and colorectal cancer

Studies have suggested that chronic inflammation may play a significant role in colorectal carcinogenesis, establishing this mechanism as one of the hallmarks of cancer [37-38]. Regarding this pathway, there are many examples in the medical literature that explain the basis of the link between some interleukins, especially IL-17, and the carcinogenesis of colorectal cancer.

Some of these links may include: enhanced interleukin-17 transcripts expression stepwise along the adenoma-carcinoma sequence in the stroma and adenomatous/cancerous intestinal epithelium of CRC patients [39]; increasing effect of IL-17 in the production of metalloproteinase MMP9 [40], whose role in malignancy progression is well documented [41-43].

While IL-17A is likely to be cancer-promoting, IL-17F may play a tumor-suppressive role, possibly via inhibiting tumor angiogenesis. Although its mechanisms are not completely understood, its expression was found to be decreased in colon câncer tissues, confirming the CRC-suppressing hypothesis [44].

The mechanism of IL-17 in tumor initiation and progression is still not fully elucidated, but in a way, most studies consider that all members of the IL-17 family favor tumor progression, although IL17F has an anti-tumor action [44]. In light of these aspects, the increased expression of IL-17 in the serum of patients with CCR raises the possibility that it can be used as a diagnostic and prognostic marker, a scenario in which high levels of the cytokine would indicate a poor prognosis [16].

In terms of cancer therapies, recent literature shows that IL-17 secreted by immune or tumor cells acts by infiltrating the tumor and promoting resistance mechanisms – suppression of apoptosis and desensitization to anti-cancer agents, VEGF for example [45, 46].

Several studies have already investigated IL-17 as a therapeutic target in the treatment of colorectal cancer [47-49]. Some of the drug options to be used in combination are monoclonal antibodies that target the cytokinesecukinumab and ixecizumab, for example, molecules that can inhibit the differentiation of the Th17 lymphocyte, molecules that can reduce production or block IL-17 downstream [49].

Another approach that deserves attention is the transfer of tumor-specific adoptive Th17 cells. Such a therapeutic approach is based on the concept demonstrated by several studies that Th17 cells can exhibit antitumor properties when adequately potentiated.

2. Conclusion

Several factors related to lifestyle or hereditary disorders can increase the risk of CRC development. After the establishment of the tumor, the immune system goes into action with the proliferation of lymphocytes which produced cytokines such as IL-17. IL-17 is a pro-inflammatory cytokine, which is associated with cancer progression. The main source of IL-17 is a subpopulation from $CD4^{+}$T cells known as T-helper17 (Th17) cells. Therefore, the role of IL-17 in the prognosis of CRC patients is still uncovered and more studies are needed. Various therapeutics have been developed for the treatment of CRC. The therapeutics include monoclonal antibodies that target IL-17 or IL-17R and molecules that can inhibit Th17 differentiation or inhibit the stimulation of IL-23 or can reduce IL-17 production. A better understanding of the physiological role of IL-17 in the regulation of these diseases may provide avenues for the development of IL-17-based therapeutic strategies.

Author contributions

BN, GF, GGZ, LV, SLP, VBL, GD and LMVN were involved in the drafting of the manuscript. LMVN, GD and RFL were involved in critical revision.

Declaration of interest

No potential conflict of interest was reported by the author (s).

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The authors declare that they have no competing interests to disclose.

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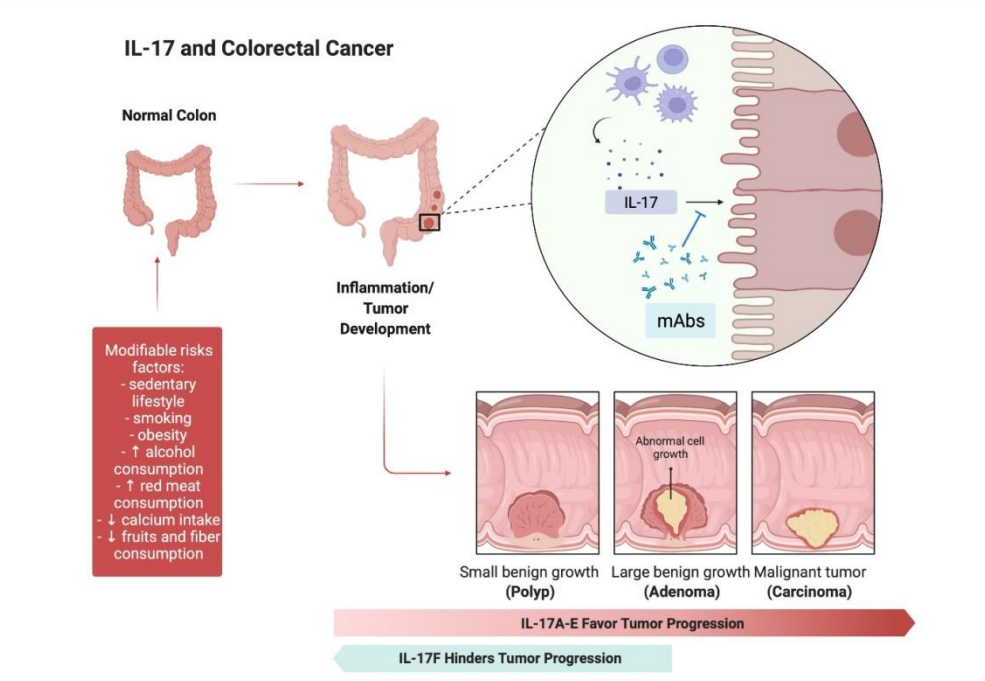

Figure 1: Modifiable factors risks are able to induce alterations in the normal colon leading to inflammation associated to the development of colorectal cancer. The development of this cancer usually goes through 3 stages: the formation of a polyp, an adenoma, and finally a carcinoma. Interleukin-17 (IL-17) is a pleiotropic proinflammatory cytokine that can promote inflammation by recruiting monocytes and neutrophils. Monoclonal antibodies (mAbs) that target inflammatory cytokines (such as IL-17) are an important therapeutic alternative for the treatment of this cancer. (IL-17, interleukin-17; mAbs, monoclonal antibodies).