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Interleukin 21 impairs tumor immunosurveillance of colitis-associated colorectal cancer

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The pathogenesis of colitis-associated colorectal cancer is strongly influenced by immune cells, cytokines and other immune mediators present in the inflamed colon. Current research has emerged that T helper cell associated cytokines play a prominent role in tumor growth. In our recent manuscript we have revealed that the Th17 associated cytokine IL-21 prominently influences tumor development and immunosurveillance of colitis-associated colorectal cancer.

Longstanding inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn disease (CD) have an increased risk to develop colorectal cancer.[1] This association of IBD with colorectal cancer was first described by Crohn et al. in 1925.[2] Chronic inflammation promotes carcinogenesis by inducing gene mutations and epigenetic alterations, alteration of the expression of factors involved in carcinogenesis (p53, APC, K-ras, Bcl-2, NFκB, COX-2, DNA mismatch— or base-excision repair proteins), releasing of reactive oxygen and nitrogen species, inhibiting apoptosis or stimulating angiogenesis and cell proliferation. The role of the immune system during the process of cancer development is multifactorial and complex. Whereas some immune cells are able to elicit protumoral effects others diminish tumor progression as part of the antitumoral immune response. However, this extensive network of tumor immune responses is far from completely understood. Among hematopoietic cells which can regulate cancer pathogenesis T cells play a prominent role. Thus, $CD4^+$ T cells as well as $CD8^+$ T cells and regulatory T cells can influence the tumor micromilieu. With this regard T cell subsets especially Th17 cells seem to be a potential target for new immunotherapeutic approaches to treat colitis-associated colorectal cancer as these cells were shown to have prominent functions in mucosal immunity. Th17 cells are termed according to their secretion of the cytokine IL-17A and are a distinct proinflammatory CD4 effector T-cell lineage.[3] Besides the secretion of IL-17A Th17 cells secrete the cytokines IL-17F, IL-21 and IL-22. The secretion of these Th17 cell-associated cytokines leads to the induction of chemokines, matrix metalloproteinases as well as antimicrobial peptides in the surrounding tissue, leading to inflammation and recruitment of neutrophils and macrophages, but less is known about the function of these cytokines in cancer development.

Among Th17-associated cytokines IL-21 seems to represent an interesting target for immunotherapeutic approaches as IL-21 is able to tip the balance between Th1 and Th17 cells.[4] IL-21 is able to impact both innate and adaptive immune responses due to its ability to act on multiple immune cells expressing the IL-21 receptor like B cells, NK cells, activated T cells, DCs, macrophages as well as fibroblasts and epithelial cells. Upon engagement of its receptor IL-21 signals through JAKs, STAT3 and ultimately Bcl-6, Tcf7, Lef1, Blimp-1 and c-Maf. Therewith IL-21 is able to influence the differentiation, cell fate, proliferation and survival of diverse immune cell subsets. As mentioned above IL-21 promotes the differentiation of Th17 cells whereas it limits the development of Tregs and effector $CD8^+$ T cells. It has been shown that IL-21 is overexpressed in the gut of patients with UC and CD compared with healthy controls[5] but also in tumors of UC-associated cancer.[6] In mouse models of intestinal colitis it was shown that IL-21 exaggerates intestinal acute colitis and that IL-21 is expressed in tumor-infiltrating lymphocytes in a colitis-associated cancer model.[6]

In our recent study our aim was to investigate the function of IL-21 during the development of colitis-associated tumorigenesis and its importance in tumor immunosurveillance.[7] We analyzed the course of chronic colitis in IL-21 deficient mice. Likewise to the acute colitis, we observed a dampened inflammation associated with intact colon architecture and decreased proliferation of intestinal cells in IL-21-deficient mice compared with wild-type (WT) mice due to diminished levels of IFNγ and IL-17. Opposing to previous results in the acute colitis, we found no alterations in Tregs levels in IL-21-deficient mice during chronic colitis.[8] Surprisingly, when we combined chronic colitis with tumorigenesis, IL-21 deficient mice showed a similar extent of inflammation compared with wild-type mice but less tumor burden. The tumors from IL-21 deficient mice were also reduced in

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diameter. This effect was due to low tumor cell proliferation and high tumor cell apoptosis in IL-21-deficient mice. The intestinal cytokine milieu of IL-21 deficient mice with colitis-associated colorectal cancer showed a decrease in IL-17, while IFNγ is highly upregulated, which in turn mediated the severe intestinal inflammation. Simultaneously, the Th17 inducing cytokine IL-23 was elevated in WT mice whereas the Th1 inducing cytokine IL-12p70 was upregulated in IL-21-deficient mice. Other protumoral cytokines like IL-6 and IL-22 remain unchanged in IL-21-deficient mice. This cytokine switch from a Th17-dominated cytokine milieu toward a Th1-dominated one happens during the transition phase from acute to chronic intestinal inflammation and is based on epithelial-derived factors that are stimulating antigen-presenting cells to induce this specific adaptive immune responses. In our studies we could verify that the increased IFNγ levels are the reason for an enhanced antitumor response mediated by $CD103^{+}CD8^{+}$ cytotoxic cells specific for tumor cells. These $CD103^{+}CD8^{+}$ T cells were elevated in IL-21-deficient mice in the course of colitis-associated tumorigenesis. Further these cells showed an enhanced cytotoxic potential against E-cadherin^{high}-expressing tumor cells. In a similar subsequent study Stolfi et al. additionally showed reduced infiltration of alternatively activated macrophages, myeloid derived suppressor cells and reduced phosphorylation of STAT3 and diminished levels of Bcl-X_L in IL-21 deficient mice.[6]

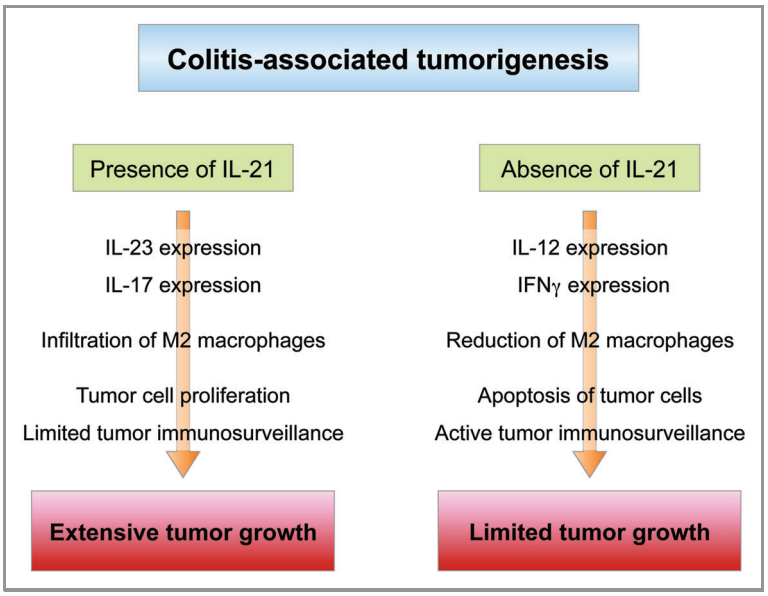

Figure 1. Schematic overview of the characteristics of an IL-21 deficient in comparison to an IL-21 rich tumor milieu.

In conclusion, our results clearly elucidate that IL-21 has a prominent function in tumor growth and immunosurveillance of colitis-associated tumorigenesis. IL-21 controls the balance between Th17 and Th1 cell subsets and therewith is necessary for the homeostasis of a tumor-supportive microenvironment characterized by extensive inflitration of Th17 cells. In addition, IL-21 controls the development of cytotoxic $CD103^{+}CD8^{+}$ T cells whose cytotoxic capacity is also diminished in the presence of IL-21.

References

1. Terzić J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010; 138: 2101-14, e5; PMID:20420949; http://dx.doi.org/10.1053/j.gastro.2010.01.058
2. Kraus S, Arber N. Inflammation and colorectal cancer. Curr Opin Pharmacol 2009; 9:405-10; PMID: 19589728; http://dx.doi.org/10.1016/j.coph.2009.06.006
3. Annunziato F, Romagnani S. Heterogeneity of human effector CD4+ T cells. Arthritis Res Ther 2009; 11:257; PMID:20053303; http://dx.doi.org/10.1186/ar2843
4. Yi JS, Cox MA, Zajac AJ. Interleukin-21: a multifunctional regulator of immunity to infections. Microbes Infect 2010; 12:1111-9; PMID:20817119; http://dx.doi.org/10.1016/j.micinf.2010.08.008
5. De Nitto D, Sarra M, Pallone F, Monteleone G. Interleukin-21 triggers effector cell responses in the gut. World J Gastroenterol 2010; 16:3638-41; PMID: 20677335; http://dx.doi.org/10.3748/wjg.v16.i29.3638
6. Stolfi C, Rizzo A, Franzè E, Rotondi A, Fantini MC, Sarra M, et al. Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. J Exp Med 2011; 208:2279-90; PMID:21987656; http://dx.doi.org/10.1084/jem.20111106
7. Jauch D, Martin M, Schiechl G, Kesselring R, Schlitt HJ, Geissler EK, et al. Interleukin 21 controls tumour growth and tumour immunosurveillance in colitis-associated tumorigenesis in mice. Gut 2011; 60: 1678-86; PMID:21948944; http://dx.doi.org/10.1136/gutjnl-2011-300612
8. Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol 2007; 37:3155-63; PMID: 17918200; http://dx.doi.org/10.1002/eji.200737766