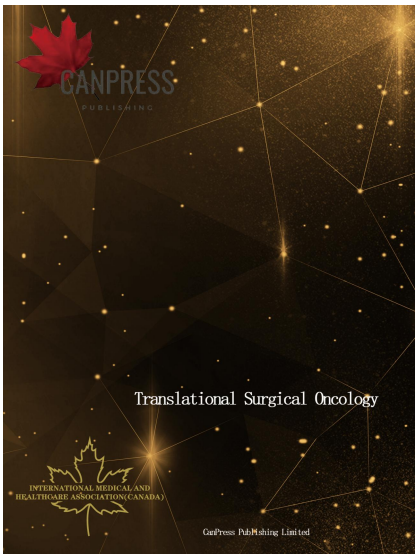
The role of interleukin 13 receptor alpha 2 in inflammatory bowel disease and colorectal cancer



Jian Lu , Benno Traub , Marko Kornmann*

Department of General and Visceral Surgery, Ulm University Hospital

*Corresponding Author Email:marko.kornmann@uniklinik-ulm.de.

Abstract

The therapeutic potential of interleukin 13 receptor alpha 2 (IL-13Rα2) has aroused considerable interest. IL-13Rα2 has long been considered to be a decoy receptor, but subsequent investigations have demonstrated that IL-13Rα2 also plays a crucial role in various inflammatory diseases and malignancies. IL-13Rα2 is capable of regulating several signaling pathways with the respective biological consequences. In this review, we summarize the role of IL-13Rα2 in inflammatory bowel disease and colorectal cancer in order to provide an updated insight into therapeutic application of IL-13Rα2.

Keywords: IL-13Rα2 , Inflammatory bowel disease , Colorectal cancer

Introduction

Colorectal cancer（CRC）is the fourth most prevalent kind of malignancy and the second cause of cancer-associated death in the United States[1]. The therapeutic potential of interleukin 13 receptor alpha 2 (IL-13Rα2) have attracted increasing attention lately. IL-13Rα2 was once thought to serve as a decoy receptor that strongly bound exogenous IL-13 without producing signaling and would consequently act as an IL-13 "neutralizer" through effectively internalizing extra IL-13 from the environment outside of the cells. However, later studies on IL-13Rα2 have revealed that this receptor chain is not exclusively a decoy receptor[2].

IL-13Rα2 is a molecule involved in inflammation and functions as a decoy receptor to sequester IL-13, or as a receptor that could mediate downstream signaling. In fact, the IL-13/IL-13Rα2 pathway offers signaling assistance that can directly convert inflammation into cancer development and metastasis[3]. In this review, we summarize the connection between IL-13Rα2 and CRC as well as inflammatory bowel disease (IBD), and discuss the role of IL-13Rα2 in the pathogenesis of IBD and CRC. Based on these, we propose therapeutic potential of IL-13Rα2 in the treatment of IBD and CRC.

Methods

We conducted a search of the Pubmed database by MeSH terms for “IL-13Rα2” in combination with “inflammatory bowel disease” or “colorectal cancer” or “colon cancer” or “rectal cancer”, “inflammatory bowel disease” in combination with “colorectal cancer” or “colon cancer” or “rectal cancer” up to October 2022. Duplicate articles were deleted, and additional articles were discovered by searching the publications' references. Following a preliminary examination of abstracts, about 198 publications were selected for review. This review covers online articles and published manuscripts. The figures used in this review were drawn online at www.figdraw.com.

IL-13Rα2

IL-13Rα2 was originally identified from a cell line derived from human renal cell cancer (Caki-1). IL-13Rα2 has a very specific binding capability for IL-13 with a short intracellular structural domain[4]. There are three types of IL-13Rα2: cytoplasmic, surface membrane, and dissolved state. However, very little is known about the distribution and interregulation of IL-13Rα2 and its different variants[5]. One study showed that the larger part of IL-13Rα2 is found intracellularly,

although it has the potential to be brought to the cell membrane in response to cytokine stimulation[6]. Figure 1 shows the structure of IL-13Rα2 (modified according to reference[3]).

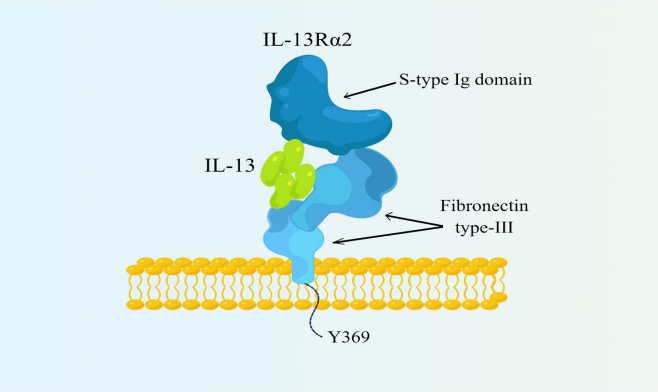


Figure 1: Structural diagram of IL-13Rα2. The IL-13Rα2 molecule is made up of three extracellular domains and has a tyrosine (Y369) in its cytoplasmic tail. The tyrosine tail is an important component for signaling.

The affinity between IL-13Rα2 and IL-13 is extremely high; the capacity of IL-13Rα2 for binding IL-13 is 500 pM, which is 5000 times more than that of IL-13Rα1[7]. The cells which express IL-13Rα2 are considered IL-13 scavengers because they are able to eliminate IL-13 from the culture medium, thereby inhibiting its activity[8]. IL-13Rα2 connects with several intracellular transport proteins, and its repossession is closely regulated to modulate expression level on surface membrane and the quantity of free receptor[9]. It is not entirely clear whether different concentrations of IL-13 help drive the transition from acute inflammation to chronic, moving IL-13Rα2 from decoys to receptors which have signal transduction abilities[3].

The binding of IL-13 with IL-13Rα2 promotes many signaling pathways to increase migration, invasion, and proliferation of CRC cells[10] A number of questions concerning the factors that drive IL-13Rα2 expression, along with its arrangement by IL-13 and its capacity for signaling, continue to be unanswered or are plagued by contradictory results as a result of their location at the intersection of a great number of different fields (immunology, allergy, infection, inflammation and cancer)[3].

Inflammatory bowel disease

IBD is a long-standing disease of the intestines that is typically classified into two subtypes: Crohn's disease (CD) and ulcerative colitis (UC)[11]. Globally, the morbidity of IBD is growing, with a frequency of around 0.5% in the western nations[12].

The pathophysiology of IBD is multifactorial; in some genetically susceptible individuals, IBD is caused by environmental factors that alter the gut microbiota and thereby trigger inflammation due to excessive immune response[13]. It is thought that CD and UC are caused by distinct immunological processes, with a Th1/Th17 response mediating CD and a Th2-type response causing UC[14-15]. Animal models have convincingly proven the role of microbiota in the etiology of IBD and intestinal cancers. In animal models, colitis develops under a typical environment but not in sterile circumstances devoid of commensal microorganisms[16-17].

UC is typically characterized by inflammation of the superficial mucosa of the colon, which progresses in a continuous manner towards the proximal end. This subsequently leads to ulceration, bleeding, fulminant colitis and toxic megacolon. In contrast, CD can affect any region of the gastrointestinal tract and is usually discontinuous. Characterized by inflammation of the permeable wall, CD can lead to problems such as fistulas, abscesses and fibrotic strictures[18].

Over 240 genetic risk variations combine with epigenetic, immunological, and microbiological factors to cause the profuse clinical symptoms of IBD[18]. Fatigue is a serious clinical issue for IBD patients, affecting over 80% of those with active illness and approximately 50% of those in clinical remission. The decreased quality of life, decreased productivity, and impaired function that come from weariness considerably raise social cost[19].

Colorectal cancer

CRC is approximately 10% of all malignancies and associated fatalities identified each year. CRC is the second most prevailing malignancy in women and the third most prevalent malignancy in males[20]. It is anticipated that the number of new cases of CRC will get 2.5 million worldwide by 2035, with the majority of new cases occurring in developing nations[21].

It is generally believed that the reduction of tumor morbidity and mortality is mainly due to the improvement of early screening and treatment methods[22]. Stabilizing and declining trends are typically only observed in highly developed nations. These are mostly a result of national screening programs and improved colonoscopy adoption. Nevertheless, changes in lifestyle and food may also be responsible[23]. Several major lifestyle factors, including smoking, alcohol abuse, obesity, and overconsumption of red and processed meat, increase the risk of CRC[21].

Polyps are considered to be the most common cause of CRC. The process begins with abnormal colonic crypts and progresses to cancerous precursor lesions known as polyps and, about 10 to 15 years later, to CRC. Currently, stem cells or stem cell-like cells are believed to be the origin of most colorectal malignancies. These cancer stem cells arise from a steady accumulation of genetic and epigenetic changes[21].

Patients with CRC may experience a variety of symptoms and signs, including changes in bowel habits, anemia or stomach upset, and even rectal bleeding. However, patients with CRC usually do not have any symptoms in the early stages unless

CRC is already advanced[21].

Numerous governments and areas of the world have embraced CRC screening programs due to their great potential to reduce morbidity and mortality[24]. The surgical procedure is the essential component of the curative treatment. The effectiveness of surgery for CRC is extremely important and may be evaluated based on a number of objective measures. Research on postoperative imaging has demonstrated that there is room for improvement in the overall standard of surgical care[25].

The relationship between IBD and CRC

IBD that has been lasted for a long period of time is one of the risk factors for CRC. The risks of acquiring colorectal cancer were 2% at 10 years following a diagnosis of UC, 8% at 20 years, and 18% at 30 years, according to a major meta-analysis on the risk of CRC in IBD patients27. Studies have established the essential cumulative impact of inflammation in raising the risk of CRC linked with IBD, and observational studies have demonstrated that the progress of colitis-associated colorectal cancer（CACRC）risk is directly connected to the degree, duration, and intensity of inflammation[26-28].

Primary sclerosing cholangitis and a family history of CRC, as well as the severity of UC are all variables that increase the likelihood of developing colon cancer[26,29,30]. Frequently, dysplasia caused by persistent inflammation develops to malignancy in IBD patients. Consequently, cancer is typically seen in the colitis-affected section of the colon[31]. Figure 2 shows the risk and protective factors for progression to advanced colorectal neoplasia in patients diagnosed with IBD[32].

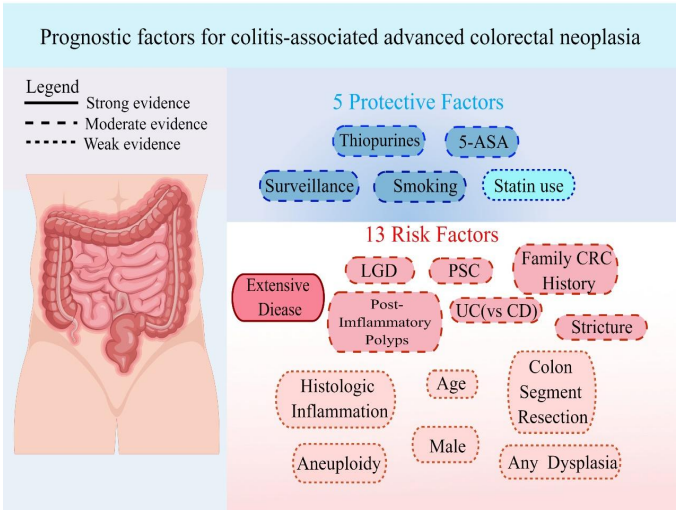


Figure 2: The 13 risk variables and 5 protecting factors for the progression of advanced colorectal neoplasia in IBD patients were found by an all-inclusive systematic review and meta-analysis[32].

There are significant clinical differences between CACRC and sporadic CRC. CACRC tends to affect younger patients with an average age of onset of 50-60 years compared to a mean age of 65-75 years for sporadic CRC[27,33,34]. Patients with IBD are more likely to have synchronous tumors[35,36]. This finding may be well explained by the connection between the features of the distribution of colitis, inflammation, heterogeneous hyperplasia, and the development of cancer[31].

The continuing destruction of local tissue caused by inflammation and the continuous replacement of damaged tissue with newly healed tissue both significantly enhance the risk of developing a tumor. This is especially true in patients who have IBD, since the accumulated possibility of getting CRC greatly increases with the passage of time until IBD is diagnosed[37]. Patients with CD are more likely than those with UC to present with advanced tumor stages, i.e. stages III or IV. Consequently, more CD patients receive palliative surgery as opposed to curative treatment[38]. Recurrent mucosal inflammation is the primary cause of IBD-related CRC, and it may be associated with a more aggressive tumor pathological character, which may affect survival rates[39].

Patients diagnosed with UC or CD are encouraged to take part in a surveillance program in order to identify and remove heterogeneous lesions before they develop into advanced colorectal neoplasia (aCRN), highly heterogeneous hyperplasia (HGD), or CRC[32]. For those who have IBD, it is vital to accurately assess and explain the risk of CRC in order to improve patient outcomes[40].

IL-13Rα2 and IBD

UC and CD are long-term gastrointestinal inflammatory diseases, both induced by an overreaction response of the immune system to the gut microbiota of a specific genetically susceptible host[41]. CD patients who had their initial symptoms displayed an active type 1 immune signature on the gut mucosa, but those with chronic illness moved to a more polarized type 2 environment, according to the findings of Kugathasan[42].

All epithelial cells in tissue samples obtained from individuals with UC and CD had an intensified IL-13Rα2 staining. This was most prominent at the bottom of the crypt, with cells near the terminals of the villi exhibiting slightly weaker staining[43]. Colitis symptoms reduced in correlation with the downregulation of IL-13Rα2 expression[2,44]. A study showed that IL-13Rα2 may cause IBD by interfering with goblet cell function and preventing epithelial healing after injury, and the reduction or even absence of IL-13Rα2 could accelerate mucosal healing[43].

Previous studies have demonstrated that the non-invariant NKT cells in the lamina propria are related with UC[15,45]. UC is defined by the existence of NKT cells expressing IL-13Rα2, suggesting that IL-13Rα2 can act as a target to differentiate UC from other types of IBD. In addition, since IL-13-producing NKT cells could be the major effector cells that promote inflammation of UC, targeting IL-13Rα2 may be a novel approach in the treatment of UC[46]. Studies have shown that the expression of IL-13Rα2 is negatively linked with the phosphorylation of STAT-6[47-49]. As STAT-6 is

essential for goblet cell proliferation and intestinal mucosal healing, it is important for intestinal mucosal repair[50,51]. The observation of goblet cell hyperplasia in mice lacking IL-13Rα2 is not unexpected44. Despite the fact that goblet cell hyperplasia and mucus production worsen asthma [52], these intestinal symptoms are really beneficial protective features[53,54].

In the last two decades, the development of anti-tumor necrosis factor (TNF) medicines has significantly improved the treatment of IBD[55]. Although the general reaction to anti-TNF medication is positive, about 30 percent of patients are non-responders[56]. In individuals with IBD, ileocolonic mucosal IL-13Rα2 mRNA expression is one important indicator of non-response to infliximab treatment[43]. In patients diagnosed with CD, ileocolonic IL-13Rα2 expression has been established as a predictor of infliximab non-response (IFX). Mucosal IL-13Rα2 expression is a possible marker for treatment selection, given its specificity in predicting resistance to anti-TNF therapy[57].

IL-13Rα2 and CRC

The relationship between IL-13Rα2 expression and worse prognosis in individuals with metastatic colon cancer was demonstrated by the observation of a considerable increase in IL-13Rα2 expression in advanced human CRC tissues[10]. In roughly 66% of immunohistochemically examined cases of CRC, IL-13Rα2 expression was elevated, with a significant link to T3 and T4 staging[58]. This poorer prognosis may be due to the more aggressive and homing ability of those cells overexpressing IL-13Rα2. Targeting certain cytokines or regulatory molecules may be an effective approach to prevent CRC metastasis and recurrence[10].

The expression of IL-13Rα2 was upregulated in highly metastatic cells[59]. The downregulation of IL-13Rα2 expression in a highly metastatic cell line resulted in a decrease in cell adhesion and a reduction in hepatic homing, suggesting that this receptor is important in the adherence, motility, invasion, and metastatic colonization of cancer cells[10].

Summary

IL-13Rα2 is gaining attention as a possible therapeutic target for malignancies. Many investigations are concentrating on developing targeted cancer treatments that attack IL-13Rα2. New therapeutic approaches based on active immunity, such as peptide, DNA, or dendritic cell vaccines, have been developed in light of the antigenic properties of IL-13Rα2 and have been validated in various clinical trials[3]. There have been some promising developments in the clinical application of CAR T cells and dendritic cell vaccines in the treatment of glioblastoma multiforme (GBM) and other types of malignancies[3].

The expression of IL-13Rα2 is particularly significant for malignancies that are linked to an inflammatory milieu. Certain subtypes of GBM, CRC, and ovarian cancer are excellent examples[60]. One study based on mouse model of colitis revealed that IL-13 conferred protection by dampening the inflammatory response of T helper cells that had a mixture of types 1 and 17. This protective effect was decreased by IL-13Rα2, showing that inhibiting IL-13Rα2 has potential as a possible therapeutic target for IBD[61].

In conclusion, IL-13Rα2 has the potential to be a therapeutic target for cancers associated with inflammation, and a comprehensive understanding of its biological features can assist in the development of more effective treatment options that target IL-13 and IL-13Rα2 in the future.

Acknowledgements

We would like to express our gratitude to the members of the group of General and Visceral Surgery at Ulm University Hospital for their insightful suggestions. The China Scholarship Council provided financial backing for this project (J.L.).

Funding project

This project was supported by China Scholarship Council (201906090390).

Comflict of interest

All authors disclosed no relevant relationship.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.

[2] Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, Kitani A. IL-13 signaling through the IL-13alpha2 receptor is involved in induction of TGF-beta1 production and fibrosis. *Nat Med.* 2006;12(1):99-106.

[3] Jaen M, Martin-Regalado A, Bartolome RA, Robles J, Casal JI. Interleukin 13 receptor alpha 2 (IL13Ralpha2): Expression, signaling pathways and therapeutic applications in cancer. *Biochim Biophys Acta Rev Cancer.* 2022;1877(5):188802.

[4] Caput D, Laurent P, Kaghad M, et al. Cloning and characterization of a specific interleukin (IL)-13 binding protein structurally related to the IL-5 receptor alpha chain. *J Biol Chem.* 1996;271(28):16921-16926.

[5] Daines MO, Tabata Y, Walker BA, et al. Level of expression of IL-13R alpha 2 impacts receptor distribution and IL-13 signaling. *J Immunol.* 2006;176(12):7495-7501.

[6] Daines MO, Hershey GK. A novel mechanism by which interferon-gamma can regulate interleukin (IL)-13 responses. Evidence for intracellular stores of IL-13 receptor alpha -2 and their rapid mobilization by interferon-gamma. *J Biol*

Chem. 2002;277(12):10387-10393.

[7] Bartolome RA, Martin-Regalado A, Jaen M, et al. Protein Tyrosine Phosphatase-1B Inhibition Disrupts IL13Ralpha2-Promoted Invasion and Metastasis in Cancer Cells. *Cancers (Basel).* 2020;12(2).

[8] Kasaian MT, Raible D, Marquette K, et al. IL-13 antibodies influence IL-13 clearance in humans by modulating scavenger activity of IL-13Ralpha2. *J Immunol.* 2011;187(1):561-569.

[9] Bartolome RA, Jaen M, Casal JI. An IL13Ralpha2 peptide exhibits therapeutic activity against metastatic colorectal cancer. *Br J Cancer.* 2018;119(8):940-949.

[10] Barderas R, Bartolomé RA, Fernandez-Aceñero MJ, Torres S, Casal JI. High expression of IL-13 receptor α2 in colorectal cancer is associated with invasion, liver metastasis, and poor prognosis. *Cancer Res.* 2012;72(11):2780-2790.

[11] Graham DB, Xavier RJ. Pathway paradigms revealed from the genetics of inflammatory bowel disease. *Nature.* 2020;578(7796):527-539.

[12] Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol.* 2015;12(12):720-727.

[13] Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol.* 2010;28:573-621.

[14] Zhang Z, Zheng M, Bindas J, Schwarzenberger P, Kolls JK. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. *Inflamm Bowel Dis.* 2006;12(5):382-388.

[15] Heller F, Fuss IJ, Nieuwenhuis EE, Blumberg RS, Strober W. Oxazolone colitis, a Th2 colitis model resembling ulcerative colitis, is mediated by IL-13-producing NK-T cells. *Immunity.* 2002;17(5):629-638.

[16] Sartor RB. Microbial influences in inflammatory bowel diseases. *Gastroenterology.* 2008;134(2):577-594.

[17] Elson CO, Cong Y, McCracken VJ, Dimmitt RA, Lorenz RG, Weaver CT. Experimental models of inflammatory bowel disease reveal innate, adaptive, and regulatory mechanisms of host dialogue with the microbiota. *Immunol Rev.* 2005;206:260-276.

[18] Chang JT. Pathophysiology of Inflammatory Bowel Diseases. *N Engl J Med.* 2020;383(27):2652-2664.

[19] Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nat Rev Gastroenterol Hepatol.* 2019;16(4):247-259.

[20] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.

[21] Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet.* 2019;394(10207):1467-1480.

[22] Weinberg BA, Marshall JL, Salem ME. The Growing Challenge of Young Adults With Colorectal Cancer. *Oncology (Williston Park).* 2017;31(5):381-389.

[23] Ait Ouakrim D, Pizot C, Boniol M, et al. Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. *BMJ.* 2015;351:h4970.

[24] Brenner H, Hoffmeister M. Striving to optimize colorectal cancer prevention. *Nat Rev Gastroenterol Hepatol.* 2021;18(10):677-678.

[25] Bondeven P, Hagemann-Madsen RH, Laurberg S, Pedersen BG. Extent and completeness of mesorectal excision evaluated by postoperative magnetic resonance imaging. *Br J Surg.* 2013;100(10):1357-1367.

[26] Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut.* 2001;48(4):526-535.

[27] Rutter MD, Saunders BP, Wilkinson KH, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology.* 2006;130(4):1030-1038.

[28] Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med.* 1990;323(18):1228-1233.

[29] Askling J, Dickman PW, Karlen P, et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. *Gastroenterology.* 2001;120(6):1356-1362.

[30] Jayaram H, Satsangi J, Chapman RW. Increased colorectal neoplasia in chronic ulcerative colitis complicated by primary sclerosing cholangitis: fact or fiction? *Gut.* 2001;48(3):430-434.

[31] Ullman T, Odze R, Farraye FA. Diagnosis and management of dysplasia in patients with ulcerative colitis and Crohn's disease of the colon. *Inflamm Bowel Dis.* 2009;15(4):630-638.

[32] Wijnands AM, de Jong ME, Lutgens M, et al. Prognostic Factors for Advanced Colorectal Neoplasia in Inflammatory Bowel Disease: Systematic Review and Meta-analysis. *Gastroenterology.* 2021;160(5):1584-1598.

[33] Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol.* 2012;10(6):639-645.

[34] Baars JE, Kuipers EJ, van Haastert M, Nicolai JJ, Poen AC, van der Woude CJ. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. *J Gastroenterol.* 2012;47(12):1308-1322.

[35] Delaunoit T, Limburg PJ, Goldberg RM, Lymp JF, Loftus EV, Jr. Colorectal cancer prognosis among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2006;4(3):335-342.

[36] Choi PM, Zelig MP. Similarity of colorectal cancer in Crohn's disease and ulcerative colitis: implications for carcinogenesis and prevention. *Gut.* 1994;35(7):950-954.

[37] Grivennikov SI, Wang K, Mucida D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature.* 2012;491(7423):254-258.

[38] Kiran RP, Khoury W, Church JM, Lavery IC, Fazio VW, Remzi FH. Colorectal cancer complicating inflammatory bowel disease: similarities and differences between Crohn's and ulcerative colitis based on three decades of experience. *Ann Surg.* 2010;252(2):330-335.

[39] Lu C, Schardey J, Zhang T, et al. Survival Outcomes and Clinicopathological Features in Inflammatory Bowel Disease-associated Colorectal Cancer: A Systematic Review and Meta-analysis. *Ann Surg.* 2022;276(5):e319-e330.

[40] Bopanna S, Ananthakrishnan AN, Kedia S, Yajnik V, Ahuja V. Risk of colorectal cancer in Asian patients with ulcerative colitis: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2017;2(4):269-276.

[41] de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol.* 2016;13(1):13-27.

[42] Kugathasan S, Saubermann LJ, Smith L, et al. Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease. *Gut.* 2007;56(12):1696-1705.

[43] Verstockt B, Perrier C, De Hertogh G, et al. Effects of Epithelial IL-13Ralpha2 Expression in Inflammatory Bowel Disease. *Front Immunol.* 2018;9:2983.

[44] Fichtner-Feigl S, Young CA, Kitani A, Geissler EK, Schlitt HJ, Strober W. IL-13 signaling via IL-13R alpha2 induces major downstream fibrogenic factors mediating fibrosis in chronic TNBS colitis. *Gastroenterology.* 2008;135(6):2003-2013, 2013 e2001-2007.

[45] Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. *J Clin Invest.* 2004;113(10):1490-1497.

[46] Fuss IJ, Joshi B, Yang Z, et al. IL-13Ralpha2-bearing, type II NKT cells reactive to sulfatide self-antigen populate the mucosa of ulcerative colitis. *Gut.* 2014;63(11):1728-1736.

[47] Hsi LC, Kundu S, Palomo J, et al. Silencing IL-13Ralpha2 promotes glioblastoma cell death via endogenous signaling. *Mol Cancer Ther.* 2011;10(7):1149-1160.

[48] Papageorgis P, Ozturk S, Lambert AW, et al. Targeting IL13Ralpha2 activates STAT6-TP63 pathway to suppress breast cancer lung metastasis. *Breast Cancer Res.* 2015;17(1):98.

[49] Shibasaki N, Yamasaki T, Kanno T, et al. Role of IL13RA2 in Sunitinib Resistance in Clear Cell Renal Cell Carcinoma. *PLoS One.* 2015;10(6):e0130980.

[50] Khan WI, Blennerhasset P, Ma C, Matthaei KI, Collins SM. Stat6 dependent goblet cell hyperplasia during intestinal nematode infection. *Parasite Immunol.* 2001;23(1):39-42.

[51] Cosin-Roger J, Ortiz-Masia D, Calatayud S, Hernandez C, Esplugues JV, Barrachina MD. The activation of Wnt signaling by a STAT6-dependent macrophage phenotype promotes mucosal repair in murine IBD. *Mucosal Immunol.* 2016;9(4):986-998.

[52] Oh CK, Geba GP, Molfino N. Investigational therapeutics targeting the IL-4/IL-13/STAT-6 pathway for the treatment of asthma. *Eur Respir Rev.* 2010;19(115):46-54.

[53] Finkelman FD, Shea-Donohue T, Morris SC, et al. Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. *Immunol Rev.* 2004;201:139-155.

[54] Inagaki-Ohara K, Sakamoto Y, Dohi T, Smith AL. gammadelta T cells play a protective role during infection with Nippostrongylus brasiliensis by promoting goblet cell function in the small intestine. *Immunology.* 2011;134(4):448-458.

[55] Verstockt B, Ferrante M, Vermeire S, Van Assche G. New treatment options for inflammatory bowel diseases. *J Gastroenterol.* 2018;53(5):585-590.

[56] Flamant M, Roblin X. Inflammatory bowel disease: towards a personalized medicine. *Therap Adv Gastroenterol.* 2018;11:1756283x17745029.

[57] Verstockt B, Verstockt S, Creyns B, et al. Mucosal IL13RA2 expression predicts nonresponse to anti-TNF therapy in Crohn's disease. *Aliment Pharmacol Ther.* 2019;49(5):572-581.

[58] Bartolome RA, Garcia-Palmero I, Torres S, Lopez-Lucendo M, Balyasnikova IV, Casal JI. IL13 Receptor alpha2

Signaling Requires a Scaffold Protein, FAM120A, to Activate the FAK and PI3K Pathways in Colon Cancer Metastasis. *Cancer Res.* 2015;75(12):2434-2444.

[59] Valverde A, Povedano E, Montiel VR, et al. Electrochemical immunosensor for IL-13 Receptor alpha2 determination and discrimination of metastatic colon cancer cells. *Biosens Bioelectron.* 2018;117:766-772.

[60] Zabolotny JM, Kim YB, Welsh LA, Kershaw EE, Neel BG, Kahn BB. Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo. *J Biol Chem.* 2008;283(21):14230-14241.

[61] Danese S. IBD: of mice and men-shedding new light on IL-13 activity in IBD. *Nat Rev Gastroenterol Hepatol.* 2011;8(3):128-129.