# MINIREVIEWS

1. Omicron variant (B.1.1.529) of SARS-CoV-2: Mutation, infectivity, transmission, and vaccine resistance  
   *Ren SY, Wang WB, Gao RD, Zhou AM*

12. Hepatitis B virus reactivation in rheumatoid arthritis  
   *Wu YL, Ke J, Zhang BY, Zhao D*

23. Paradoxical role of interleukin-33/suppressor of tumorigenicity 2 in colorectal carcinogenesis: Progress and therapeutic potential  
   *Huang F, Chen WY, Ma J, He XL, Wang JW*

# ORIGINAL ARTICLE

**Case Control Study**

35. Changes in rheumatoid arthritis under ultrasound before and after sinomenine injection  
   *Huang YM, Zhuang Y, Tan ZM*

43. Benefits of multidisciplinary collaborative care team-based nursing services in treating pressure injury wounds in cerebral infarction patients  
   *Gu YH, Wang X, Sun SS*

**Retrospective Study**

51. Outcomes and complications of open, laparoscopic, and hybrid giant ventral hernia repair  
   *Yang S, Wang MG, Nie YS, Zhao XF, Liu J*

62. Surgical resection of intradural extramedullary tumors in the atlantoaxial spine *via* a posterior approach  
   *Meng DH, Wang JQ, Yang KX, Chen WY, Pan C, Jiang H*

71. Vancomycin lavage for the incidence of acute surgical site infection following primary total hip arthroplasty and total knee arthroplasty  
   *Duan MY, Zhang HZ*

79. Distribution of transient receptor potential vanilloid-1 channels in gastrointestinal tract of patients with morbid obesity  
   *Atas U, Erin N, Tazegul G, Elpek GO, Yıldırım B*

91. Value of neutrophil-lymphocyte ratio in evaluating response to percutaneous catheter drainage in patients with acute pancreatitis  
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>Influence of overweight and obesity on the mortality of hospitalized</td>
<td>Wang N, Liu BW, Ma CM, Yan Y, Su QW, Yin FZ</td>
</tr>
<tr>
<td></td>
<td>patients with community-acquired pneumonia</td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>Minimally invasive open reduction of greater tuberosity fractures by</td>
<td>Kong LP, Yang JJ, Wang F, Liu FX, Yang YL</td>
</tr>
<tr>
<td></td>
<td>a modified suture bridge procedure</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>Increased levels of lactate dehydrogenase and hypertension are</td>
<td>Jin ZM, Shi JC, Zheng M, Chen QL, Zhou YY, Cheng F, Cai J, Jiang XG</td>
</tr>
<tr>
<td></td>
<td>associated with severe illness of COVID-19</td>
<td></td>
</tr>
<tr>
<td>136</td>
<td>Age, alcohol, sex, and metabolic factors as risk factors for</td>
<td>Yan Y, Wu JS, Pan S</td>
</tr>
<tr>
<td></td>
<td>colonic diverticulosis</td>
<td></td>
</tr>
<tr>
<td>143</td>
<td>Evaluation of right-to-left shunt on contrast-enhanced transcranial</td>
<td>Xiao L, Yan YH, Ding YF, Liu M, Kong LJ, Hu CH, Hui PJ</td>
</tr>
<tr>
<td></td>
<td>Doppler in patent foramen ovale-related cryptogenic stroke: Research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>based on imaging</td>
<td></td>
</tr>
<tr>
<td>155</td>
<td>Characterization of focal hypermetabolic thyroid incidentaloma: An</td>
<td>Lee H, Chung YS, Lee JH, Lee KY, Hwang KH</td>
</tr>
<tr>
<td></td>
<td>analysis with F-18 fluorodeoxyglucose positron emission tomography/</td>
<td></td>
</tr>
<tr>
<td></td>
<td>computed tomography parameters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reduces tissue resident memory T cells in chronic eczema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with neurocognitive disorder and/or diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>189</td>
<td>Predicting adolescent perfectionism: The role of socio-demographic</td>
<td>Livazović G, Kuzmanović K</td>
</tr>
<tr>
<td></td>
<td>traits, personal relationships, and media</td>
<td></td>
</tr>
<tr>
<td>205</td>
<td>Novel m.4268T&gt;C mutation in the mitochondrial tRNA^Ile gene is</td>
<td>Zhao LJ, Zhang ZL, Fu Y</td>
</tr>
<tr>
<td></td>
<td>associated with hearing loss in two Chinese families</td>
<td></td>
</tr>
<tr>
<td></td>
<td>outcomes</td>
<td></td>
</tr>
<tr>
<td>227</td>
<td>Zinc carnosine-based modified bismuth quadruple therapy vs standard</td>
<td>Ibrahim N, El Said H, Choukair A</td>
</tr>
<tr>
<td></td>
<td>triple therapy for Helicobacter pylori eradication: A randomized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>controlled study</td>
<td></td>
</tr>
</tbody>
</table>
CASE REPORT

236 Acquired coagulation dysfunction resulting from vitamin K-dependent coagulation factor deficiency associated with rheumatoid arthritis: A case report
Huang YJ, Han L, Li J, Chen C

242 Intraoperative thromboelastography-guided transfusion in a patient with factor XI deficiency: A case report
Guo WJ, Chen WY, Yu XR, Shen L, Huang YG

249 Positron emission tomography and magnetic resonance imaging combined with computed tomography in tumor volume delineation: A case report
Zhou QP, Zhao YH, Gao L

254 Successful response to camrelizumab in metastatic bladder cancer: A case report
Xie C, Yuan X, Chen SH, Liu ZY, Lu DL, Xu F, Chen ZQ, Zhong XM

260 HER2 changes to positive after neoadjuvant chemotherapy in breast cancer: A case report and literature review
Wang L, Jiang Q, He MY, Shen P

268 Hyper-accuracy three-dimensional reconstruction as a tool for better planning of retroperitoneal liposarcoma resection: A case report
Ye MS, Wu HK, Qin XZ, Luo F, Li Z

275 Recurrent postmenopausal bleeding - just endometrial disease or ovarian sex cord-stromal tumor? A case report
Wang J, Yang Q, Zhang NN, Wang DD

283 Complex proximal femoral fracture in a young patient followed up for 3 years: A case report
Li ZY, Cheng WD, Qi L, Yu SS, Jing JH

289 Bilateral Hypertrophic Olivary Degeneration after Pontine Hemorrhage: A Case Report
Zheng B, Wang J, Huang XQ, Chen Z, Gu GF, Luo XJ

296 Clinical characteristics and outcomes of primary intracranial alveolar soft-part sarcoma: A case report
Chen JY, Cen B, Hu F, Qiu Y, Xiao GM, Zhou JG, Zhang FC

304 Removal of laparoscopic cerclage stitches via laparotomy and rivanol-induced labour: A case report and literature review
Na XN, Cai BS

309 Cerebral venous sinus thrombosis in pregnancy: A case report
Zhou B, Huang SS, Huang C, Liu SY

316 Eustachian tube teratoma: A case report
Li JY, Sun LX, Hu N, Song GS, Dou WQ, Gong RZ, Li CT
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>331</td>
<td>Lunate dislocation with avulsed triquetral fracture: A case report</td>
<td>Li LY, Lin CJ, Ko CY</td>
</tr>
<tr>
<td>361</td>
<td>Diagnostic and surgical challenges of progressive neck and upper back painless masses in Madelung’s disease: A case report and review of literature</td>
<td>Yan YJ, Zhou SQ, Li CQ, Ruan Y</td>
</tr>
<tr>
<td>371</td>
<td>Suspected cerebrovascular air embolism during endoscopic esophageal varices ligation under sedation with fatal outcome: A case report</td>
<td>Zhang CMJ, Wang X</td>
</tr>
<tr>
<td>381</td>
<td>An atypical primary malignant melanoma arising from the cervical nerve root: A case report and review of literature</td>
<td>Shi YF, Chen YQ, Chen HF, Hu X</td>
</tr>
<tr>
<td>388</td>
<td>Epidural blood patch for spontaneous intracranial hypotension with subdural hematoma: A case report and review of literature</td>
<td>Choi SH, Lee YY, Kim WJ</td>
</tr>
</tbody>
</table>
ABOUT COVER
Editorial Board Member of World Journal of Clinical Cases, Ravi Kant, MD, Associate Professor, Division of Endocrinology, Diabetes and Metabolism, Medical University of South Carolina/Anmed Campus, Anderson, SC 29621, United States. rkant82@hotmail.com

AIMS AND SCOPE
The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING
The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC’s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Lin-YuTong Wang; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Bao-Gan Peng

EDITORS-IN-CHIEF MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
January 7, 2022

COPYRIGHT
© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/gerinfo/239

ONLINE SUBMISSION
https://www.f6publishing.com
Paradoxical role of interleukin-33/suppressor of tumorigenicity 2 in colorectal carcinogenesis: Progress and therapeutic potential

Fang Huang, Wan-Yuan Chen, Jie Ma, Xiang-Lei He, Jian-Wei Wang

ORCID number: Fang Huang 0000-0002-3115-8703; Wan-Yuan Chen 0000-0002-8216-9568; Jie Ma 0000-0003-7555-996X; Xiang-Lei He 0000-0002-2559-0049; Jian-Wei Wang 0000-0003-1671-4780.

Author contributions: Huang F and Wang JW contributed to the conception and design of the paper, literature review; Huang F, Chen WY, and Ma J searched the literature and wrote the paper; Huang F drew the picture and table, and Huang F, He XL and Wang JW revised the paper.

Conflict-of-interest statement: The authors declare no conflict of interest.

Supported by Natural Science Foundation of China, No. 81803069; Zhejiang Medical Technology Plan Project, No. 2019RC007, No. 2019KY007 and No. 2021KY047; and Funds of Science Technology Department of Zhejiang Province, No. LGF21H160033.

Country/Territory of origin: China

Specialty type: Biochemistry and molecular biology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Abstract

Colorectal cancer (CRC) is presently the second most prevalent global mortality-inducing cancer. CRC carcinogenesis is a multifactorial process involving internal genetic mutations and the external environment. In addition, non-neoplastic cell activities within tumor microenvironments for CRC development have been established. However, interleukin (IL)-33, secreted by such cell types, plays a pivotal role in cancer progression due to interaction with cellular constituents within the tumor-inflammation microenvironment. IL-33 belongs to the IL-1 cytokine family and acts as binding attachments for the suppressor of tumorigenicity (ST)2 receptor. Therefore, how to coordinate tumor microenvironment, design and optimize treatment strategies suitable for CRC, based on IL-33/ST2 signaling is a challenge. Even though it has established influences upon immunity-linked conditions, IL-33 effects on CRC progression and prevention and related mechanisms are still controversial. Our review depicts controversial activities for IL-33/ST2 within carcinogenesis and cancer prevention. Moreover, IL-33/ST2 signaling is a potential therapeutic target for CRC.

Key Words: Interleukin 33; Suppressor of tumorigenicity 2 signaling; Tumor microenvironment; Conventional therapies; Colorectal cancer

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Interleukin (IL)-33 belongs to the IL-1 cytokine family and binds to the
suppressor of tumorigenicity (ST)2 receptor. IL-33 plays a key role in cancer progression due to interaction with cellular components in the inflammatory microenvironment of tumors. Therefore, it is a challenge to design and optimize treatment strategies suitable for colorectal cancer (CRC) based on IL-33/ST2 signaling to coordinate the tumor microenvironment. IL-33 also has effects on CRC prevention. These findings implicate multifaceted roles of IL-33 in cancer treatment.

**INTRODUCTION**

During 2020 alone, approximately 19.3 million newly diagnosed cancer cases were recorded, together with nearly 10 million global cancer mortalities\[1\]. Stemming from such statistics, colorectal cancer (CRC) represents the third most prevalent tumor (10%), and the second most prevalent global mortality-inducing cancer (9.4%)\[1\]. Approximately 10% of all CRC cases are inherited, with over 90% being sporadically randomized. In general, tumor initiation and development are primarily determined by key factors, such as genetic instability, epigenetic changes, antiapoptotic activity, immune-system circumvention, invasiveness, and metastases\[2\]. Three mechanisms of genetic instability in sporadic CRC have been identified: CpG-island methylation phenotype, chromosomal-based imbalances, and microsatellite instabilities. In particular, it is worth mentioning that several risk factors are related to CRC development, including lack of exercise, smoking, and red meat and alcohol consumption\[3\]. In addition, obesity, type 2 diabetes and inflammatory bowel disease (IBD) are highly linked to exacerbated CRC development. The parts played by non-neoplastic cells within tumor microenvironments (TMEs) for cancer development have been identified\[2,4\]. The cytokines, growth factors, and hormones secreted by these non-neoplastic cells are pivotal in cancer progression by interaction with the cellular constituents within tumor inflammation microenvironments\[5\]. Such cytokines include interleukin (IL)-33, a member of the IL-1 cytokine superfamily, which has been shown to mainly invoke T-helper (Th)2 immune response activities by means of its suppressor of tumorigenicity (ST)2 receptor\[6\]. IL-33/ST2 signal transduction is involved in IBD, maintenance of tissue homeostasis, and tumor invasion\[7,8\]. IL-33 can be pro- or antitumorigenic in CRC, with both activities indicating that IL-33 plays vital roles in enrolling immune-system cell types to modulate TMEs. In this review, IL-33/ST2 involvement in colorectal carcinogenesis, progress and therapeutic potential are discussed.

**DISCOVERY AND STRUCTURE OF IL-33 AND ITS LIGAND ST2**

IL-33 was first identified in 2003. It is highly upregulated within hypertrophic veins as a nuclear protein, and given its first name, nuclear factor, from high endothelial venules\[9\]. Later in 2005, IL-33 was recognized as a member of the IL-1 cytokines family\[6\]. Meanwhile, IL-33 was recognized to be a ligand for ST2 receptor\[6\]. The molecular full-length weight for human IL-33 is 30 kDa. This cytokine has 270 amino acid residues, while murine IL-33 has only 266\[6\]. Human IL-33 consists of three domains: the N-terminal (aa 1–65), which is important for chromatin-binding and nuclear localization; central (aa 66–111), which interacts with nuclear factor-B; and C-terminal IL-1-like cytokine domain (aa 112–270), including the region binding to ST2 \[10\]. After synthesis, IL-33 is passively released following cellular mechanical-stress/damage triggers\[11\]. Meanwhile, the precursor protein IL-33 is cleaved to produce the 10-fold-active matured version, compared to full-length IL-33, and is segmented to effectively activate group 2 innate lymphoid cells (ILC2s)\[12,13\].

**Citation:** Huang F, Chen WY, Ma J, He XL, Wang JW. Paradoxical role of interleukin-33/suppressor of tumorigenicity 2 in colorectal carcinogenesis: Progress and therapeutic potential. *World J Clin Cases* 2022; 10(1): 23-34

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i1/23.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i1.23
The ST2 receptor was first recognized as an oncogene in murine fibroblasts[14,15]. It has been investigated for many years before establishment of ligand IL-33, so ST2 was previously considered to be orphan receptor. The ST2 receptor derives from IL-1RL, which is a type-1 transmembrane protein[14]. Four ST2 isoforms are produced by alternative splicing, such as ST2L (ligand), sST2, ST2V (variant), and ST2LV (ligand variant). ST2L is a membrane-anchored receptor similar to IL-1, having three immunoglobulin-like extracellular, transmembrane domains, together with IL-1R1-like intracellular domains[16,17], sST2 is a soluble-secreted isoform of ST2 that has no transmembrane domain, although it carries an extracellular domain as ST2L, with 5–9 extra amino acids on the C terminus in humans and mice[16,18]. ST2V resembles sST2 and lacks the third extracellular domain, although it has a hydrophobic tail instead of a third immunoglobulin-like domain[19]. ST2LV is an additional soluble isoform with no transmembrane domain[20], ST2L and sST2 have been thoroughly investigated, although knowledge is scarce about ST2V and ST2LV. ST2L is typically expressed on fibroblasts, mast cells, Th2 lymphocytes, dendritic cells and macrophages, and sST2 is mainly present on fibroblasts/epithelial cells[20].

ROLES OF IL-33/ST2 IN CRC

IL-33/ST2 and CRC carcinogenesis

Like most malignant tumors, CRC carcinogenesis involves multiple factors and processes. For most sporadic CRC, the important causes of CRC carcinogenesis are adenomas, intestinal polypl deterioration, tumor suppressor gene APC (adenomatous polyposis coli) mutation and TME formation[21]. Recently, many studies have shown that IL-33/ST2 plays a vital role in CRC occurrence and progression[22]. Cui et al[23] reported that the IL-33/ST2 axis promoted the neoplastic transformation of human colorectal adenoma to CRC, which is closely correlated with increased IL-33 expression in CRC tissues as compared to adjacent noncancer tissues.

Another study found that IL-33 acts as a mediator of intestinal polyposis and regulator of tumor stromal cell activation in Apc(min/+)-mice, a genetic model of intestinal tumorigenesis[24]. In the Apc(min/+)-polyps, IL-33 is expressed in tumor epithelial cells, and ST2 is related to two stromal cell types, subepithelial myofibroblasts and mast cells. Stimulation of IL-33 induces stromal cells to express components of the extracellular matrix and growth factors that promote tumor development and growth[24]. He et al[25] reported that epithelial IL-33 promotes intestinal tumorigenesis in Apc(min/+)-mice with transgenic expression of IL-33 in intestinal epithelial cells through the expansion of ST2+ T regulatory (Treg) cells, Th2 cytokine production and alternative activation of macrophages. Conversely, loss of IL-33 or ST2 in Apc(min/+)-mice inhibits tumorigenesis and tumor angiogenesis, and induces apoptosis in adenomatous polyps[24,25]. This suggests that IL-33 promotes the transition of adenomas and polyposis to CRC through the activation of tumor stromal cells and the formation of a protumorigenic microenvironment.

The TME plays important roles in triggering cancer. The alarm protein IL-33 has been shown to be involved in formation of the early TME and to influence carcinogenesis and progression. Pastille and colleagues used animal models and patient samples to suggest that IL-33/ST2 axis activity restricted effector CD8+ T cell functions in the CRC environment and promoted tumor growth in the colon[26]. In addition, IL-33 downregulates IL-17 and differentiation through forkhead box (FOX)P3, indicating an immunosuppressive environment during CRC tumorigenesis[26]. In murine models for colon cancer, IL-33 within tumor regions can recruit and activate macrophages into the microenvironment, leading to prostaglandin E2 upregulation, consequently exacerbating colon cancer stemness/progression[27]. IL-33/ST2 signaling can activate c-Jun and stem cell genes (NANOG, NOTCH3 and OCT3/4) to induce CRC stemness, eventually to promote carcinogenesis[27]. More importantly, Taniguchi et al[28] reported the potential role of IL-33 in regulating tumor-initiating cells, as well as the impact on stem cell–niche interactions, which is necessary for tumor progression, and highlighted the new role of IL-33 in promoting CRC stemness and carcinogenesis.

IL-33/ST2 and CRC progression

A major hallmark for CRC progression is chronic inflammation[29]. IL-33 is upregulated within serum of ulcerative colitis cases, and consequently involved in the development and maintenance of inflammation. Meanwhile, ulcerative colitis is intimately linked to CRC progression, indicating that IL-33 has a pivotal role in...
triggering colon tumors[30]. Kirsten and colleagues suggested that involvement of the IL-33/ST2 axis was critical for CRC progression using bone marrow chimera investigations. This is partly because activation of the IL-33/ST2 signaling pathway damages intestinal barrier integrity, inducing immune-system cells to express protumorigenic IL-6[31]. Therefore, there is now compelling evidence that IL-6 serum level is linked to late-stage CRC in patients, together with being a predictor for poor prognosis in CRC[32].

It is also reported that epidermal growth factor (EGF) is a powerful signaling molecule, affecting CRC progression and intestinal epithelial cell development[33–35]. IL-33 and ST2 expression profiles can be strongly stimulated by EGF, without increasing the extracellular secretion of IL-33. Consequently, IL-33 upregulation leads to CRC triggering, thus indicating that the EGF/IL-33/ST2 axis components are novel drug targets against CRC[36]. In addition, CRC triggering/progress can be influenced through the immune microenvironment[37–39]. Multiple investigations have indicated that IL-33 thwarts host-based tumor immunity, tumor stroma modulation and exacerbation of angiogenesis, thus contributing to IL-33 receptor ST2-driven CRC[40].

Recently, IL-33/Treg cell interaction has attracted increasing attention. An early study showed that IL-33 can promote Treg cell function in the colorectum, where FOXP3+ Treg cells are abundant[41]. Treg cells can resist dysregulated inflammatory responses, and consequently acquire tissue-specific survival and function. It is well known that TME-resident IL-33 and Treg cells in the TME are individually implicated within CRC progression, albeit this is still in dispute. IL-33/ST2 signaling exacerbates CRC progression through modulation of FOXP3+ Treg cell phenotypic features and curtailing IL-17 differentiation[26]. Furthermore, tumor-derived IL-33 can remodel the TME through the recruitment of CD11b+/Gr1+ and CD11b+/F4/80+ myeloid cells and promote CRC growth and liver metastasis in mice, with the potential as a therapeutic target[42]. IL-33 also has a pivotal effect on Treg cell functional stability, with genetic deletion of IL-33 improving the effectiveness of cancer immunotherapies[43].

**IL-33/ST2 and CRC prevention**

IL-33 is considered to have a cancer-promoting role because IL-33/ST2 axis induction leads to CRC carcinogenesis/development. However, another concern is that IL-33 has a paradoxical role. Selected studies have indicated that IL-33 has a less-known role of tumor suppressor within many malignant tumors[44,45].

The IL-33/ST2 signaling pathway usually induces Th2-cell-derived expression of IL-4, IL-5 and IL-13. IL-33 is also involved in cellular immunity-related responses through upregulating IL-4 and interferon (IFN)-γ by CD8+ T, invariant natural killer (NK)T cells and NK cells, together with amplifying Th1-oriented immune responses[46–48]. Thus, it shows that IL-33/ST2 signaling plays two roles in tumorigenesis – stimulating tumor growth or inhibiting tumor progression.

In aspects of cancer prevention, tumoral IL-33 overexpression increases antitumoral responses by the immune system, together with tumor rejection through activation of CD8+ T/NK cells[49]. Furthermore, Treg cell depletion synergizes with re-expression of IL-33 to contribute cancer-eliminating Th1-type immunity-related actions, implicating that IL-33 is a promising antitumor cytokine for immunotherapy[49].

Another study implied a protective role for IL-33/ST2 against CRC invasiveness and metastases, resulting in reduced colorectal tumor growth[50]. Malik et al[30] have demonstrated that IL-33-lacking mice are sensitive to colitis-associated cancer (CAC). Meanwhile, this study highlighted that IL-33, IgA, IL-1α and the microbiota are candidate drug targets against IBD/CAC.

Many studies have shed light on IL-33 functions, whereas the literature on ST2 in CRC is scarce. Antitumorigenic functions of the IL-33 receptor have been gradually explained in CRC since 2016. Akimoto and co-workers have reported that soluble sST2 negatively correlated with colon tumor malignant growth in vivo by modifying the TME[51]. They further revealed the mechanisms: sST2 inhibited IL-33-driven angiogenesis, macrophage infiltration/polarization, and Th1 and Th2 activities. Another study by Donnell and colleagues demonstrated that ST2L downregulation in colon cancer, together with elevated tumor grade, led to ST2L downregulation. Colon-tumor-resident ST2 knockdown led to increased tumor expansion in animal studies, with a decrease in IL-33-driven macrophage infiltration and enrollment through antagonizing chemokine CCL2[52]. This indicates that IL-33 has an antitumor function against CRC and the IL-33/ST2 axis exerts protective functions against colon-based tumor-triggering.

Consequently, negative functions for the IL-33/ST2 axis in CRC progression depend on its involvement in the induction of angiogenesis, regulation of anti-tumor-based immunity-related responses and TME modulation[53]. Additional studies are needed...
to validate the precise functions adopted by IL-33/ST2 signaling in CRC (Figure 1).

DIVERSIFIED THERAPEUTICS BASED ON IL-33/ST2 SIGNALING IN CRC

IL-33 is related to carcinogenesis, progression and poor prognosis in some cancers, including CRC [40]. Due to TME-resident IL-33/ST2 variability, their overexpression/recombinant protein inhibits CRC expansion. This suggests the potential of the IL-33/ST2 axis as a drug target for CRC. Many studies have reported possible strategies for the treatment of CRC based on the IL-33/ST2 axis (Table 1).

IL-33/ST2 and conventional therapies

Intestinal mucositis and severe diarrhea are commonly associated with cancer chemotherapy and are thus dose-limiting adverse effects. Combining radiation with conventional chemotherapy can exacerbate mucositis, leading to chemotherapeutic dose reductions or inevitable cessation of such treatments [54]. Since chemotherapy directly results in DNA damage/apoptosis through reactive oxygen species (ROS) and variation of cytokine production [55], as a proinflammatory factor, IL-33 has a pivotal part in driving inflammation/tumors through its ST2 receptor. One particular investigation highlighted that IL-33, in reduced doses, resisted chemotherapeutic platinum-drug-induced cell death and enhanced cellular invasiveness in selected tumors through JNK pathway triggering [56]. Thus, regulation of the IL-33/ST2 pathway can relieve inflammation/improve chemotherapy function.

Irinotecan (CPT-11) is a topoisomerase I inhibitor, and is an antitumor drug that can be used to treat metastatic CRC [57,58]. The clinical pharmacokinetics of CPT-11 and its metabolites such as SN-38 seem to be the key factor for optimal use of anticancer chemotherapeutic drugs [57]. CPT-11 systemic-based treatment causes intense mucosal disruption and diarrhea, coinciding with small intestinal IL-33 upregulation. However, the symptoms of mucositis were markedly lower within ST2+/ mice. Recombinant IL-33 protein reinforces CPT-11-driven mucositis, and blockade of IL-33 with its complementary antibody (or soluble ST2) significantly alleviates mucositis and reduces tumor growth by CPT-11 in a mouse model of CT26 colon cancer [59]. Such results indicate that thwarting the IL-33/ST2 axis can be exploited as a novel therapy against mucositis, consequently enhancing the beneficial effect of chemotherapy against CRC.

IL-33/ST2 and treatment with immune-checkpoint inhibitor

Immunotherapy represents a powerful method in cancer treatment. Stemming from this, immune checkpoint modulation has been broadly applied to treat multiple cancers, following the discovery of cytotoxic T lymphocyte-associated protein 4 and programmed cell death (PD)-1 [60,61], which was awarded the 2018 Nobel Prize in Physiology or Medicine. Blockade of immune checkpoint yields promising clinical results in CRC. However, only a subset of cancer patients having an elevated microsatellite instability frequency phenotype develop durable antitumor immune responses due to the complicated TME associated with PD-1 and PD ligand (PD-L)1 [62,63]. It can be explained from recent data that IL-33/ST2 can regulate PD-1/PD-L1 signaling within tumors. For example, exogenous IL-33 upregulated PD-1 by CD8+ T cells, together with upregulated PD-L1 within murine acute myeloid leukemia (AML) cells [64]. Thus, combining IL-33 with PD-1 antibody dramatically extends AML murine survival times in a CD8+ T-cell-based fashion, even leading to full regression within 50% of such treated mice. Another study showed that IL-33 triggered CD8+ T cells/ILC2s in pancreatic tumors, and activated ILC2s increased PD-1 expression. Subsequent combined treatment of IL-33 and PD-1 inhibition enhanced immunotherapy outcomes in a murine model [65].

Recent results showed that IL-33/ST2 act as candidate targets of checkpoint inhibitors for CRC immunotherapy, where they are secreted by lymphocytes, stromal cells and tumor cells to recruit immune cells and remodel the tolerogenic TME. A recent study reported that ST2 is specifically expressed in tumor-associated macrophages (TAMs) of CRC, and ST2 upregulation is related to low survival odds and reduced CD8+ T cell cytotoxicity in CRC [66]. They also found that ST2-positive TAMs were enrolled into CRC xenograft model tumors through chemokine receptor CXCR3, promoting an immunosuppressive TME. Thus, the combined effect of ST2 depletion using ST2-knockout mice and treatment with PD-1 antibody had a significant suppressive effect on CRC growth. The use of IL-33 trap fusion protein reduced tumor-infiltrating ST2+ TAMs and thwarted xenograft tumor expansion in CRC preclinical models. Thus, the IL-33/ST2 axis plays a big part in CRC immuno-


**Table 1 Diversified therapeutics based on interleukin-33/suppressor of tumorigenicity 2 signaling in colorectal cancer**

<table>
<thead>
<tr>
<th>Type of therapeutic strategies</th>
<th>Pattern of IL-33/ST2 signaling involved</th>
<th>Drugs or cells used</th>
<th>Antitumor effects or mechanisms</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Therapy</td>
<td>Blockade of IL-33/ST2 signaling</td>
<td>Irinotecan, SN-38</td>
<td>Alleviated mucositis, reduced tumor growth</td>
<td>[55,59, 60]</td>
</tr>
<tr>
<td>Blockade of immune checkpoint</td>
<td>Exogenous IL-33 or its overexpression, ST2 depletion</td>
<td>PD-1 antibody</td>
<td>Activated CD8+ T cell cytotoxicity, tumor regression</td>
<td>[66,67]</td>
</tr>
<tr>
<td>Lymphocyte immunotherapy</td>
<td>Enhanced IL-33 expression</td>
<td>Tumor-infiltrating CD8+ T, IFN-γ+ CD4+ T cells, eosinophils, ILC2</td>
<td>Upregulation of IFN-γ, antitumor immunity, inhibition of tumor expansion/metastasis</td>
<td>[69,71, 73,76]</td>
</tr>
<tr>
<td>Cancer gene therapy</td>
<td>Overexpression of IL-33</td>
<td>Oncolytic adenovirus, vaccinia virus</td>
<td>Oncolyis, inhibition of tumor growth, migration and tumor stem-cell activity</td>
<td>[77,78]</td>
</tr>
</tbody>
</table>

PD-1: Programmed cell death-1; IL: Interleukin; IFN: Interferon; ST2: Suppressor of tumorigenicity 2; ILC2: Group 2 innate lymphoid cell.

**IL-33/ST2 signaling and lymphocyte immunotherapy**

Being an alarmin and immune regulation-related factor, IL-33 has a pivotal role in regulating the function of a wide range of immune cells. However, whether IL-33/ST2 signaling-regulated immune lymphocytes exert potential antitumor immunity in CRC is still a question under investigation. Recent research progress seems to suggest the positive reactivity based on Th1 cells (CD8+ T and NK cells) and Th2 cells (CD4+ T, ILC2 and eosinophils etc.).

Several studies indicated that exogenous or endogenous IL-33 is positively related to recruitment and CD8+ T/NK cell triggering within the TME. In melanoma or breast cancer models, exogenous application or transgenic expression of IL-33 recruits and activates (IFN-γ+ CD107α+ CD8+ T and NK cells to orchestrate the TME, regulates xenograft tumor expansion and prevents lung metastasis of breast cancer in mice[49, 67]. In the CRC model, Xia et al.[68] found that overall antitumor responses/IFN-γ expression by tumor-infiltrating CD8+ T cells were impaired in IL-33-deficient mice. Conversely, IL-33 upregulated IFN-γ by activated CD4+ /CD8+ T cells, improving CD8+ T cell infiltrative and antitumor responses against protumor effects by Treg cells. These results imply that the balance of CD8+ T cells and Treg cells within the TME is a crucial factor for IL-33-mediated anticancer responses in CRC.

In addition to activating Th1 response, IL-33 additionally modulate Th2 functions, including CD4+ T cells, ILC2s and eosinophils in the TME. IL-33 can directly target conventional and regulatory CD4+ T cells expressing ST2, and promote the immunosuppressive functions of Treg cells, which causes tumor growth and immune evasion[69]. IL-33 preferentially promotes Th2 response to modulate tumor immunity. In murine CT26 or MC38 CRC models, recombinant IL-33 markedly reduced colon tumor expansion/metastatic activity in lungs/liver[70]. IL-33 treatment can augment IFN-γ+ CD4+ T cells, together with upregulating CD40L on TILs. Moreover, IL-33 was found to be adequate for upregulating ST2 on CD4+ T cells, although not in CD8+ T/NK cells, suggesting that IL-33/ST2 signaling activates CD4+ T cells through positive-feedback looping.

Emerging studies have proved the positive role of eosinophils in mediating anticancer immunity-related counteractivity by IL-33 within several cancers, including CRC[71]. A more recent study by Kienzl and colleagues demonstrated that IL-33 can inhibit cancer expansion in CT26 engraftment/colitis-linked CRC mouse models[72]. The IL-33-induced effect was cancelled within eosinophil-lacking dbIGATA-1 mice, although it was rescued through adoptive transfer of ex vivo-triggered eosinophils by IL-33[72]. They further found that IL-33 treatment upregulated eosinophil biomarkers associated with triggering and homing (CD11b and Siglec-F), and with degranulation (CD63 and CD107α) in vitro and in vivo. These results implied that eosinophils are a requisite for the antitumor effect of IL-33 in CRC. Moreover, IL-33 stimulation can enrich ILC2s in the TME of many cancers, and ILC2s also constitutively express ST2 [73]. Thus, IL-33 targets directly ILC2s and induces ILC2 cell expansion, enrichment and activation in tumors[74]. Thus, it was proved that, in local expression of IL-33 in murine CRC, CT26 enhanced MyD88-based antitumor ILC2 activity[75]. In this study, IL-33 promoted production of CXCL2 from ILC2s, and created a TME with CXCR2-expressing tumor cells through a dysfunctional angiogenesis/hypoxia/ROS axis, which caused tumor cell-specific apoptosis. The finding highlights the vital role of...
ILC2s in the IL-33-mediated antitumor effect for CRC immunotherapy.

**IL-33/ST2 signaling and cancer gene therapy and other blockade strategies**

Recently, gene therapy using viral or nonviral vectors to carry therapeutic genes for diseases has attracted increased attention. In particular, breakthroughs have been made in the treatment of genetic diseases. Gene therapy also shows a promising prospect in the field of human cancer treatment. In our group, cancer gene therapy using oncolytic viruses as vectors has achieved encouraging results. We have constructed multiple oncolytic viruses targeting multiple cancers, such as CD55-Smad4 for CRC[76], GD55 for liver cancer[77,78] and Ad-wnt(24) for Wnt signaling-positive cancer[79]. In CRC, tumor-disruptive adenovirus CD55-Smad4 was developed without issues and succeeded in regulating CRC cell growth, migration, and tumor stem-cell activity through reining-in of Wnt/β-catenin signaling. Previous reports have demonstrated that recombinant ST2/IL-33 significantly inhibits CRC growth and enhances antitumor immune effects[72]. It additionally suggests that oncolytic viruses, targeting CRC and carrying IL-33 or ST2 gene, have the potential for tumor therapy through overexpression of IL-33 or ST2 gene and lysis of tumor cells mediated by oncolytic viruses. Our unpublished results showed that oncolytic adenovirus and vaccinia virus carrying the IL-33 gene can effectively inhibit the growth of mouse CT26 CRC cells in vitro, and further in vivo experiments are ongoing (Figure 2).
There are at least two anti-IL-33 antibodies (SAR440340 and MEDI3506) being developed to treat chronic obstructive pulmonary disease, moderate-to-severe asthma, and chronic bronchitis in clinical phase I and II trials (NCT03387852, NCT03546907, NCT04751487, NCT04570657, NCT04701983, and NCT04631016). Thus, it suggests that the blockade strategy using anti-IL-33 antibodies has the potential for treatment of human cancer, including CRC, where IL-33 plays the protumorigenesis role.

CONCLUSION

IL-33 plays a controversial role in carcinogenesis, cancer prevention and cancer immunity, although the specific mechanism is still unclear. In CRC, the divergent roles of IL-33 may depend on the TME. Therefore, how to orchestrate the TME to design and optimize appropriate treatment strategies based on IL-33/ST2 signaling for CRC is an important question. These strategies include how to activate and recruit IFN-γ-secreting CD4+ and CD8+ T cells, NK cells, dendritic cells, M1 macrophages, eosinophils and ILC2s, and how to better combine chemotherapy, immune checkpoint inhibitors and cancer gene therapy to achieve more effective treatments for CRC. Moreover, being an alarmin, IL-33 may take up the role of a potential biomarker for CRC diagnosis, therapy and prognosis.

REFERENCES

7 Nunes T, Bernardazzi C, de Souza HS. Interleukin-33 and inflammatory bowel diseases: lessons from


11  **Kakkar R, Hei H, Dobner S, Lee RT.** Interleukin 33 as a mechanically responsive cytokine secreted by living cells. *J Biol Chem* 2012; 287: 6941-6948 [PMID: 22215666 DOI: 10.1074/jbc.M111.297870]

12  **Lefrançais E, Roga S, Gautier V, Gonzalez-de-Peredo A, Monsarrat B, Girard JP, Cayrol C.** IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G. *Proc Natl Acad Sci U S A* 2012; 109: 1673-1678 [PMID: 22307629 DOI: 10.1073/pnas.1115841109]

13  **Lefrançais E, Duval A, Mirey E, Roga S, Espinosa E, Cayrol C, Girard JP.** Central domain of IL-33 is cleaved by mast cell proteases for potent activation of group-2 innate lymphoid cells. *Proc Natl Acad Sci U S A* 2014; 111: 15502-15507 [PMID: 25313073 DOI: 10.1073/pnas.1410701111]

14  **Tominaga S.** A putative protein of a growth specific cDNA from BALB/c-3T3 cells is highly similar to the extracellular portion of mouse interleukin 1 receptor. *FEBS Lett* 1989; 258: 301-304 [PMID: 25331553 DOI: 10.1016/0014-5793(89)81679-5]


23  **Cui G, Qi H, Gunderman MD, Yang H, Christiansen I, Sorbye SW, Goll R, Florholmen J.** Dynamics of the IL-33/ST2 network in the progression of human colorectal adenoma to sporadic colorectal cancer. *Cancer Immunol Immunother* 2015; 64: 181-190 [PMID: 25324197 DOI: 10.1007/s00262-014-1624-x]


Huang F et al. Paradoxical role of IL-33/ST2


Schiavoni G, Mattei F. Anti-Tumorigenic Activities of IL-33: A Mechanistic Insight.

Andreone S

Luo P

[PMID: 26679377] DOI: 10.1038/bjc.2015.433

Komai-Koma M

[PMID: 26679377] DOI: 10.1038/bjc.2015.433


