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Inflammasome-mediated suppression of inflammation-induced colorectal cancer progression is mediated by direct regulation of epithelial cell proliferation

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Chronic inflammation is a risk factor for many types of human cancers, yet the precise mechanism of this strong association is largely unknown. The inflammasome is a multiprotein complex that has recently been shown to orchestrate multiple innate and adaptive immune responses, yet its potential role in inflammation-induced cancer has been little studied. We recently reported a surprising link between the inflammasome and colorectal inflammation-induced tumorigenesis. In the model, the role of caspase-1 and NLRC4 in tumorigenesis was found to be mediated by direct and profound effects on colonic epithelial cell proliferation and cell death, rather than through regulation of colonic inflammation. Herein, we discuss the recent advances and discoveries related to the role of inflammasome in inflammation-induced colorectal tumorigenesis.

Key words: inflammasome, colon cancer, NLRC4, NLRP3, inflammation

Abbreviations: AOM, azoxymethane; CAC, colitis-associated colon cancer; DSS, dextran sulphate sodium; IKKβ, IκB kinase β; IBD, inflammatory bowel disease; NFκB, nuclear factor κB; NLRs, nod-like receptors; PAMPs, pattern-associated molecular patterns; TLR, toll-like receptor; TNF, tumor necrosis factor

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The innate immune arm is an evolutionarily conserved component of the immune system that enables rapid response to invading pathogens and endogenous stress signals.[1] The best-studied sensors of such stimuli are the Toll-like receptor (TLR) family, which recognize diverse pathogenic signals or pattern-associated molecular patterns (PAMPs), including lipopolysaccharide, bacterial lipoprotein, peptidoglycan, unmethylated bacterial CpG DNA, flagellin, mycobacterial lipoarabinomannan and mannans of yeasts.[2] TLR sensing of infectious agents results in activation of signaling pathways that mediate the initiation of inflammation as well as secretion of anti-infectious effector molecules. The newly discovered family of innate sensors, termed Nod-like receptors (NLRs), includes members such as NOD1, NOD2 and the NLRC4 family.[3,4] Several of the NLRs, including NLRP1, NLRP3 and NLRC4, possess the ability to form cytoplasmatic multiprotein complexes named "inflammasomes" that serve as recruitment and activation platforms to inflammatory caspases, such as Caspase-1, leading, in turn, to cleavage of the inflammatory cytokines pro-IL-1β and pro-IL-18 into their mature forms.[5,6]

Inflammasomes orchestrate multiple innate and adaptive immune responses and aberrant inflammasome formation has been linked to a variety of infectious, inflammatory and autoimmune diseases. Examples are numerous and include NLRP3 inflammasome activation by crystalline or polymeric molecules, such as gout-associated monosodium urate, atherosclerosis-associated cholesterol crystals, Alzheimer disease-related amyloid β and lung diseases-related silica and asbestos.[7-12] The NLRP3 inflammasome has also been implicated in defense response against pathogens such as Listeria, Staphylococcus and Shigella bacteria, adenovirus, influenza A and Sendai viruses as well as the fungi *Saccharomyces cerevisiae* and *Candida albicans*.[13-16] The NLRC4 inflammasome has been demonstrated to play an important role in host defense against infections from a number of Gram-negative bacterial pathogens, such as Pseudomonas,

Salmonella, Legionella and Shigella,[17-22] while the NLRP1 inflammasome has been reported to mediate host response against *Bacillus anthracis* infections.[23,24] The AIM2 inflammasome has been recently shown to mediate host response against cytosolic bacteria and DNA viruses, such as mouse cytomegalovirus, vaccinia viruses, Listeria and Francisella bacterial infection.[25-27] The role of NLRs and inflammasome in tumorigenesis and, in particular, in inflammation-induced colorectal cancer formation has been little studied.

Inflammation has been linked to the pathogenesis of tumors in up to 15% of human cancers.[28] Common examples of inflammation-induced cancers include *Helicobacter pylori* causing gastrointestinal carcinoma, Hepatitis B and C viruses causing Hepatocellular carcinoma and Human Papillomavirus causing cervical cancer.[28] One of the most widely studied and prevalent inflammation-induced cancers is Inflammatory Bowel Disease (IBD)-associated colorectal cancer.[29] IBD is a chronic autoinflammatory disorder affecting the intestinal tract that is most prevalent in developed countries.[30,31] Patients suffering from long-standing IBD have a significantly higher risk of developing colorectal cancer.[32] Suggested mechanisms for this striking association include chronic colonic inflammation producing reactive oxygen and nitrogen species that can, in turn, promote oncogenesis through DNA damage, cell proliferation or cell survival alteration by activation of cytoplasmic and nuclear signaling transduction pathways and modulation of stress-induced proteins and genes.[33-37] Further inflammation-induced contribution to tumor growth was suggested to be mediated by tumor-infiltrating immune cells that produce a variety of cytokines and chemokines that promote local inflammation, leading to enhancement of the growth and survival of premalignant epithelial cells by activating transcription factors such as NFκB.[38-40] In recent years, inflammation-induced tumorigenesis has been shown to be mediated by the transcriptional factor NFκB in both colorectal and liver inflammation-induced cancer models.[39,40] In the azoxymethane-dextran sulphate sodium (AOM-DSS) inflammation-induced colorectal cancer model, deletion of IKKβ in myeloid cells, the protein kinase required for NFκB signaling, resulted in a decrease in tumor incidence and significant reduction of the tumor size through a reduction in the pro-inflammatory cytokines IL-6 and TNFα. In parallel, deletion of IKKβ in epithelial cells was shown to decrease tumor incidence through enhancement of epithelial cell apoptosis.[40]

Several lines of evidence recently suggested that the NLR family may participate in inflammation-induced tumorigenesis, possibly through formation of inflammasomes. The NLRP3 inflammasome had been demonstrated to participate in the IL-1β-dependent adaptive immune response against dying tumor cells.[41] Specifically, the NLRP3 inflammasome in dendritic cells was shown to be activated by ATP released from chemotherapy-treated tumors, leading to an effective $CD8^+$ T-cell response directed against the tumor.[41] In addition, mice deficient in MyD88, an essential component of the TLR signaling cascade downstream of the IL-1 receptor family, were shown to exhibit reduced tumor loads in a model of intestinal tumorigenesis.[42] The phenotype could be partly explained by reduction of IL-1β and IL-18 signaling, but also might potentially stem from impaired TLR-dependent transcription of inflammasome precursors. In a recent paper, $MyD88^{-/-}$ mice and $IL\text{-}18^{-/-}$ mice were shown to develop severe chemically induced colitis and colon tumorigenesis as compared to WT mice, suggesting the crucial role of IL-18 signaling in colorectal cancer.[43] Furthermore, three recent reports suggested that deficiency in Caspase-1, ASC and NLRP3 in mice was associated with an increased severity of chemically induced colitis. The phenotype was suggested to be associated with decreased secretion of IL-1β and IL-18 both locally and systemically.[45-47] Dupaul-Chicoine et al. showed that after DSS administration, $Caspase\text{-}1^{-/-}$ ($Casp1^{-/-}$) mice exhibited defects in epithelial cell regeneration and tissue repair, increased invasion of commensal bacteria and enhanced inflammation and NFκB activation in colon tissues. The phenotype could be rescued by administration of exogenous IL-18, while $ASC^{-/-}$ mice only partially reproduced the phenotype.[46] Zaki et al. observed that NLRP3, ASC and Caspase-1-deficient mice have enhanced chemically induced colitis and increased systemic dissemination of commensal microflora, and this phenotype was suggested to be mediated by the protective role of NLRP3 inflammasome against loss of epithelial barrier integrity.[47] With regard to colon cancer, Dupaul-Chicoine et al. showed that caspase-12 deficiency, which was a dominant-negative regulator of inflammasome and the NOD-NFκB pathway, results in enhanced azoxymethane (AOM) and dextran sulfate sodium (DSS) induced tumorigenesis.[48-50] The phenotype was suggested to be associated with enhanced NFκB signaling, enhanced tissue repair after DSS injury and increased cell survival and proliferation in tumor tissue.[46] Allen et al. reported that in the AOM-DSS colitis-associated colon cancer model, NLRP3, ASC and Caspase-1-deficient mice have enhanced tumorigenesis and DSS induced colitis, a phenotype that was suggested to be mediated by the reduction of IL-1β and IL-18 production in the colon tissue during AOM-DSS treatment, and the NLRP3 inflammasome effects on tumorogenesis were suggested to mainly depend on hematopoietic cells.[45] The suggested role of NLRP3 has, however, been controversial, as, in another report, an ameliorated severity of colitis was observed in NLRP3-deficient mice in the same DSS induced colitis model, where it was suggested to be mediated by the local reduction of proinflammatory cytokines IL-1β, TNFα and IFNγ.[51] Differences between these studies may due to methodological differences as well as to inherent differences of variables, such as the composition of the intestinal flora in different facilities, as one report suggested that inflammasome component-deficient mice as $NLRP3^{-/-}$ mice may feature altered intestinal microbiota.[52]

Likewise, we hypothesized that inflammasome inactivation may directly affect inflammation-induced colorectal formation through regulation of the inflammatory reaction leading to tumorigenesis. As inflammasomes control the maturation of these two proinflammatory cytokines, we hypothesized that inflammasome

component-knockout mice may have decreased disease in the inflammation-induced colitis-associated colon cancer model when compared to wild-type mice. To our surprise, Casp1$^{-/-}$ mice were found to have increased tumorigenesis in the AOM-DSS induced colitis-associated colon cancer model, and, more surprisingly,[44] the enhanced tumorigenesis was not caused by increased inflammation in Casp1$^{-/-}$ mice but rather by the regulation of proliferation and cell death in colonic epithelial cell and tumor tissue cells. Casp1$^{-/-}$ mice have increased colonic epithelial cell proliferation in the early stage of tumorigenesis and increased tumor cell proliferation. Moreover, Casp1$^{-/-}$ mice were shown to have reduced apoptosis within tumors. We further showed that NLRC4$^{-/-}$ mice, rather than NLRP3$^{-/-}$ mice, have enhanced tumorigenesis. In NLRC4$^{-/-}$ mice, we found that proliferation was enhanced and cell death attenuated in colonic epithelial cells, suggesting that intrinsic effects in the colonic epithelial cells are the cause for the dramatic enhancement in tumor formation in knockout mice. To further validate our results, we performed bone marrow chimera experiments in which WT or NLRC4$^{-/-}$ mice were reconstituted with a WT or NLRC4$^{-/-}$ immune system. The resultant four-way chimeric mice clearly demonstrated that the NLRC4 deficiency resides in the "radio-resistant" compartment, likely the epithelial layer, and that this was responsible for the increased tumorigenesis in NLRC4$^{-/-}$ mice (**Fig. 1**). As NLRC4 has been shown to be involved in p53-dependent cell death,[53,54] it may provide a link for the reduced cell death in tumor tissue in Casp1$^{-/-}$ and NLRC4$^{-/-}$ mice.[49,50] The fact that NLRC4 inflammasome is activated by Gram-negative bacteria may provide a link between effects mediated by the gut microflora and colonic inflammation-induced tumorigenesis. Interestingly, we found caspase-1 mRNA expression to be downregulated in WT tumors in the AOM-DSS model, indicating that Caspase-1 may potentially act as a tumor suppressor in this model. In agreement with this, tumors of Casp1$^{-/-}$ and NLRC4$^{-/-}$ mice appeared more aggressive with invasion of tumor cells through the muscularis mucosae, an aggressive feature that is rarely observed in this model.

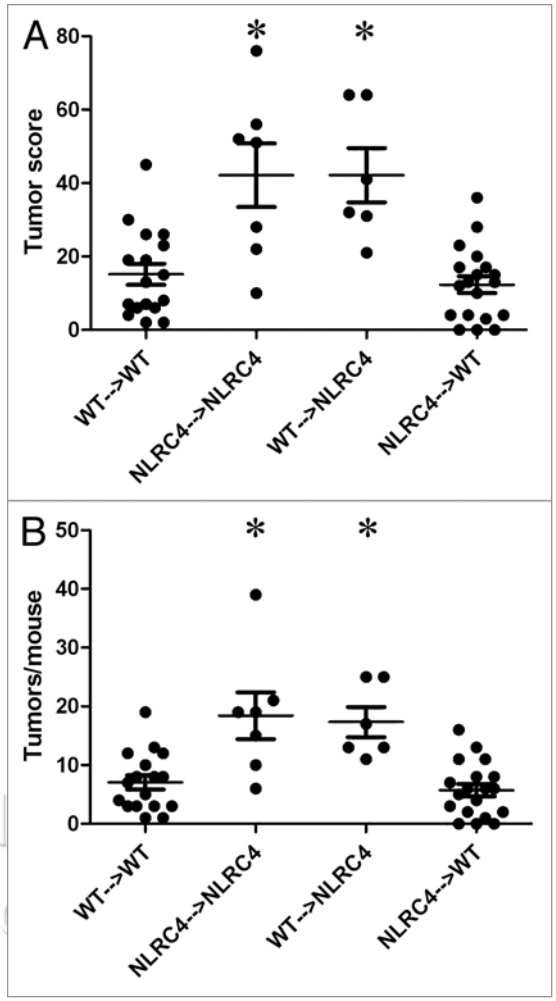

Figure 1. Mice with deficiency of NLRC4 in colonic epithelial cells develop enhanced AOM-DSS-induced tumorigenesis. WT or NLRC4$^{-/-}$ bone marrow was transferred to WT or NLRC4$^{-/-}$ mice following sublethal irradiation (two doses of 550 rad). An AOM-DSS colitis-associated colon cancer (CAC) regimen was induced 8 weeks later, as we previously described in reference 55. Tumor load (A) and tumor number/mouse (B) were determined by colonoscopy on Day 65 of the CAC regimen. Data are expressed as mean ± SEM. Differences were analyzed by one-way ANOVA and post hoc analysis for multiple group comparison. p values ≤ 0.05 were considered significant.

Despite these intriguing findings, many questions remain unanswered. What are the molecular mechanisms underlying inflammasome regulation of inflammation-induced carcinogenesis? What are the inflammasome activators upstream of the NLRC4 inflammasome whose activation regulates tumor formation in this model? What is the role of other NLRs in inflammation-induced tumorigenesis? Does inflammasome-mediated regulation of the adaptive immune response play a regulatory role? Further deciphering of these important issues may enhance our understanding to the initiation of inflammation-initiated tumorigenesis, as well as enable the recognition of new therapeutic targets.

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