



# NLRP3 inflammasome in colitis and colitis-associated colorectal cancer

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## Abstract

A low level of inflammation is an integral part of the balance between the immune system and the microbiota in the high antigen environment of the gastrointestinal tract and maintains homeostasis. A failure of this balance can lead to chronic intestinal inflammation and increase the chances to develop colorectal cancer significantly. The underlying mechanisms that link inflammation and carcinogenesis are not clear but the molecular platforms of the inflammasomes have been implicated. Inflammasomes are molecule complexes that are assembled in response to microbial components or cellular danger signals and facilitate the production of bioactive pro-inflammatory cytokines. One inflammasome in particular, NLRP3, has been analysed extensively in its contribution to colitis and has been shown to be associated with the development of colitis-associated colorectal cancer. This review will summarise the role of NLRP3 in intestinal inflammation, discuss some of the triggers of inflammation in the gastrointestinal tract such as diet and introduce some opportunities to use this inflammasome as therapeutic target for the treatment of colitis and colitis-associated colorectal cancer.

## Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide (Ferlay et al. 2015) and presents with a high mortality rate (Siegel et al. 2016) due to rapid cancer progression with late diagnosis at an advanced tumour stage (Siegel et al. 2014). An inflammation-associated form of CRC, colitis-associated CAC has been recognised as a complication of inflammatory bowel disease (IBD) (Parian and Lazarev 2015; Triantafyllidis et al. 2009). These

chronic inflammatory, idiopathic disorders are characterised by significant inflammation of small intestine and colon and are becoming more prevalent and more severe due to global adoption of western diet, the increasing use of nonsteroidal anti-inflammatory medications and an ageing population (Taleban et al. 2015). Furthermore, the increasing incidence and prevalence of IBD in children makes it an important paediatric chronic disease (Nasiri et al. 2017) with an increased risk of developing CAC (Peneau et al. 2013).

The two primary types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). CD commonly affects the small intestine or colon, however it can affect all parts of the gastrointestinal tract from the oesophagus to the anus involving all layers of the intestinal wall. Complications characteristic for CD are strictures, fistulae and fissures. UC is characterised with inflammation that is limited to the mucosa of the colon and presents with bleeding ulcers and that can result in the perforation of the colon (Cosnes et al. 2011; Mulder et al. 2014).

## Innate immunity, IBD and cancer

Crohn and Rosenberg first reported an ulcerative colitis case associated with colorectal cancer development in 1925 (Crohn and Rosenberg 1925). Subsequently, many studies have been published indicating gut inflammation

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as an important factor predisposing the development of colorectal cancer (Dupaul-Chicoine et al. 2010; Karin and Greten 2005). The cumulative risk of UC-associated cancer is estimated to be at 1.6% at 10 years, 8.3% at 20 years and 18.4% at 30 years (Eaden et al. 2001) correlating CAC directly to the extent and duration of colitis. Nevertheless the exact mechanism of how chronic inflammation is connected to the development of colitis-associated colorectal cancer (CAC) has yet to be established.

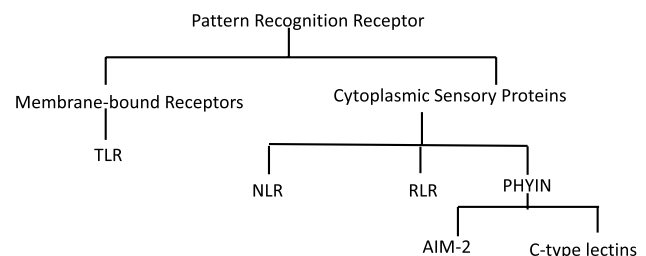
Chronic inflammation in IBD progresses to CAC with constant overproduction of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, TNF- $\alpha$  (Becker et al. 2004; Popivanova et al. 2008), chemokines and DNA damaging reactive oxygen and nitrogen species. These inflammatory effector molecules promote aberrant intestinal epithelial cell proliferation, survival and angiogenesis and lead to epithelial dysplasia and ultimately to a formation of invasive tumours (Grivennikov 2013). Therefore, understanding and modulating the mechanisms of chronic mucosal inflammation will be the key to preventing the progression to CAC (Foersch and Neurath 2014).

Although the exact aetiology of chronic intestinal inflammation is not yet known, recent studies support the hypothesis of a defective innate immune response as the primary mechanism in chronic mucosal inflammation (Asquith and Powrie 2010). The innate immune response controls the intestinal microbiota and provides initial resistance to invading pathogens whilst maintaining homeostasis (Ignacio et al. 2016). Beyond anatomical barriers such as the skin and mucosa, various cellular components of the innate immune system such as epithelial cells, macrophages, dendritic cells (DC) and neutrophils are located in the intestinal wall and intestinal lymphoid organs including Peyer's Patches and mesenteric lymph nodes. These cell populations keep the microbial occupants of the intestines under surveillance with the help of extracellular and cytosolic pattern recognition receptors (PRRs). The PRRs comprise the pro-inflammatory membrane-bound Toll-like receptors (TLR) and the cytosolic sensory protein complexes consisting of NOD-like receptors (NLR), the RNA sensing retinoic acid-inducible gene-1 receptors (RLR) and the pyrin and HIN domain (PYHIN) receptor family which includes the AIM2-like receptor (ALR) and C-type lectins (Ranson et al. 2017). These receptors recognise pathogen-associated molecular patterns (PAMPs) or host derived danger-associated molecular patterns (DAMPs). Receptor engagement causes cellular activation of various effector mechanisms ranging from microbicidal molecules and phagocytosis to activation of large multi-protein complexes called inflammasomes.

## Biology of inflammasomes

Inflammasomes have emerged as a central feature in innate immunity (Martinon et al. 2002) and are involved in pathogen clearance, maintain tissue homeostasis and stimulate an adaptive immune response that removes tumour cells. These large cytosolic protein complexes can be divided in the NLR, the PYHIN or the ALR family (Fig. 1) and comprise inflammatory caspases which undergo autocatalytic activation and initiate inflammatory signalling cascades that activate protease Caspase-1 and releases pro-inflammatory cytokines IL-1 $\beta$  and IL-18 (Latz et al. 2013; Ranson and Eri 2013). This sequence of activating events is culminating in the initiation of pyroptosis, a Gasdermin-D-mediated form of inflammatory programmed cell death (Man et al. 2017). The functionally most completely characterised family member of the NLR is the NOD-like receptor family, pyrin domain containing protein 3 (NLRP3) (Table 1).

The association of inflammasomes with intestinal inflammation and CAC has been demonstrated with expression analysis of human colon cancer samples which shows lower expression levels for *NLRP* and *AIM2* family members (Liu et al. 2015; Ranson and Eri 2013). Genetic ablation of these inflammasomes in the DSS/AOM CAC murine model suggested that they act to suppress intestinal inflammation-associated tumourigenesis essentially through inhibiting cellular proliferation and driving cell death (Allen et al. 2010, 2012; Chen et al. 2011; Karki et al. 2017; Normand et al. 2011; Wilson et al. 2015; Zaki et al. 2011). Mice deficient in inflammasome components such as apoptosis-associated speck-like protein containing a Caspase activation and recruitment domain (ASC), Caspase-1 and Caspase-11, IL-18 or IL-18r, exhibit increased colitis and tumorigenesis compared to wild-type (WT) mice in the azoxymethane-dextran sulphate sodium (AOM-DSS) model (Dupaul-Chicoine et al. 2010; Salcedo et al. 2010; Williams et al. 2015;



**Fig. 1** PRRs that initiate innate immunity. PRRs can be membrane bound like TLRs, or present in the cytoplasm as sensory proteins. The families are termed nucleotide-binding domain leucine-rich repeat containing receptors (NLRs), RIG-I like receptors and pyrin and HIN domain (PYHIN) receptors. PHYIN receptors are further subdivided as absent in melanoma (AIM2) receptors and C-type lectins

**Table 1** NLR subfamilies and their functions

Family	Subtypes	Role in immunity	References
NOD	6 subtypes	Defence against bacterial and viral infection. NLRC3 is associated with Colitis, CAC and CRC. NLRC4 has been correlated with melanoma	Janowski et al. (2013), Karki et al. (2016), Kobayashi et al. (2005), Loving et al. (2009), Viala et al. (2004), Zhang et al. (2014)
IPAF	2 subtypes	NAIP–NLRC4 together prevent against bacterial infection	Janowski et al. (2013), Zhao and Shao (2015)
NLRP	14 subtypes	Associated with defence against various bacterial and viral infection. NLRP3, 6 and 12 have been associated with colitis and CAC. NLRP3 is associated with various manifestations of metabolic syndrome	Allen et al. (2010), Anand et al. (2012), Chavarria-Smith and Vance (2015), Janowski et al. (2013), Vladimer et al. (2012), Wlodarska et al. (2014)

Zaki et al. 2010b). These studies highlight the importance of inflammasome pathways in the modulation of colitis and the suppression of CAC.

### Mechanism of action: NLRP3 in the innate immune response

Polymorphisms of the *NLRP3* gene are associated with poor survival in CAC patients and the specific role of NLRP3 in the processes leading to tumorigenesis is not well understood (Ungerback et al. 2012). Therefore, we will discuss the current literature on the specific contribution of NLRP3 to the modulation of the intestinal microbiota and intestinal pathologies of colitis and CAC.

The NLRP3 inflammasome is a multiprotein platform comprising the NLRP3 protein, the adaptor protein ASC and pro-Caspase-1. The NLRP3 protein itself contains a nucleotide-binding and oligomerization domain (NBD or NACHT), carboxy-terminal leucine-rich repeat (LRR) at the C-terminus and a PYD (Leemans et al. 2011). The inflammasome assembly is inhibited by the LRR domain. This activity is disabled by the activating signal either from PAMPS or DAMPS, whereas the NBD is required for homo- or hetero-oligomerization that leads to the activation of Caspase-1 from the inactive zymogen pro-Caspase-1 and the subsequent auto-cleavage and secretion of the pro-inflammatory cytokines IL-1 $\beta$  and IL-18 (Martinon et al. 2002, Schroder and Tschopp 2010).

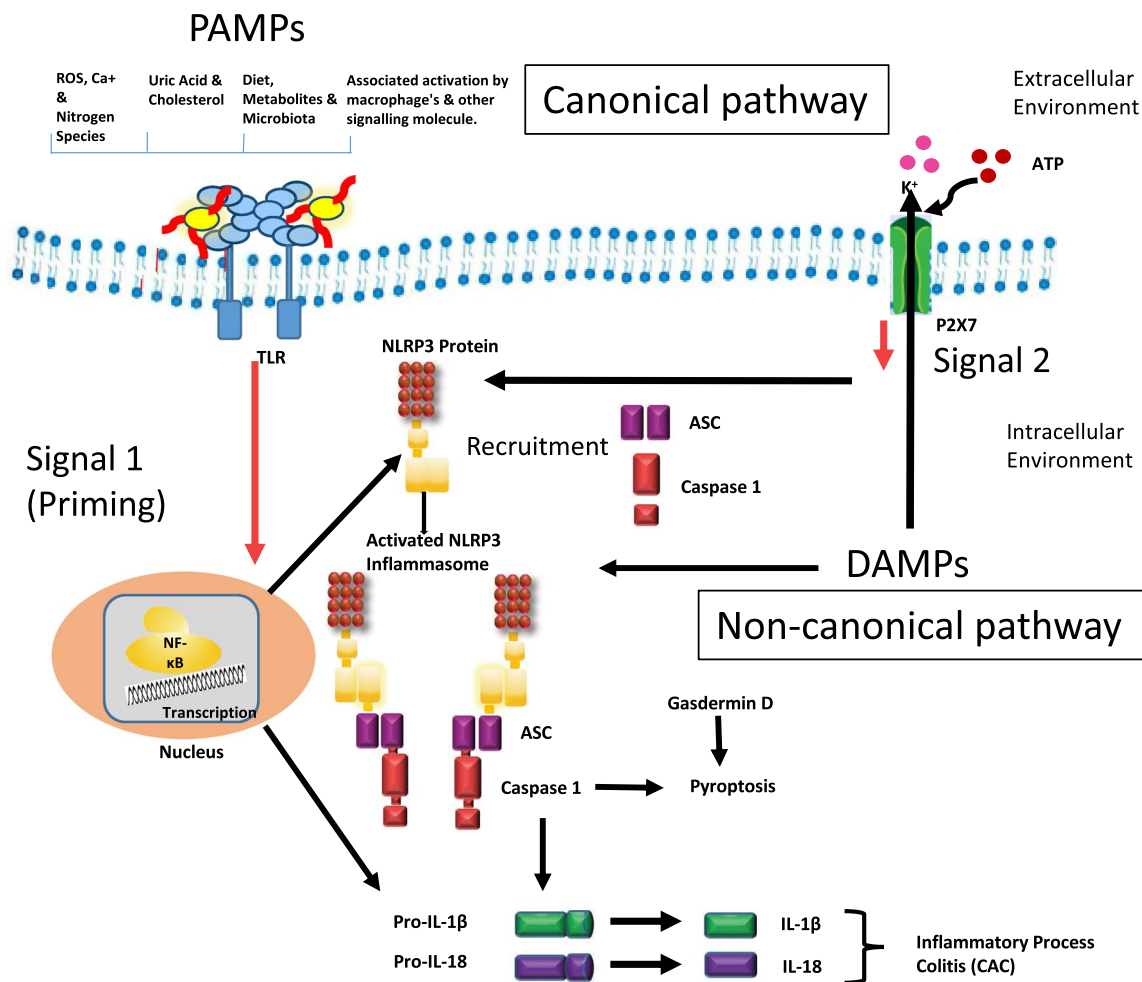
Triggers for activation of NLRP3 inflammasome include a diversified array of unrelated molecular structures (PAMPS) such as microbial cell wall components including lipopolysaccharide (LPS) and muramyl dipeptide (MDP), nucleic acids, pore-forming toxins, DAMPS, ATP and crystalline substances such as uric acid, oxidised mitochondrial DNA. As the NLRP3 inflammasome assembles in response to these molecules, it has been proposed that it responds to a common cellular distress signal, instead of a direct interaction with cognate ligands (Halle et al. 2008; Mariathasan et al. 2006; Martinon et al. 2006; Shimada et al. 2012) (Fig. 2). Three key mechanistic pathways have been suggested for

triggering the activation of NLRP3 inflammasome. Firstly, pore formation and potassium efflux (Petrilli et al. 2007), secondly, lysosomal destabilisation (Okada et al. 2014) and thirdly, mitochondrial reactive oxygen species (mROS) generation (Gurung et al. 2015). Importantly, the presence of ROS has been implicated in the activation of the NLRP3 inflammasome and has been linked to cancer promotion (Fang et al. 2009).

Canonical activation of NLRP3 occurs in two steps via both transcriptional and post-transcriptional processes. The first signal (Signal 1) is provided predominantly in a PAMPS-dependent manner. A frequently used model is the lipopolysaccharide (LPS)-induced activation of the TLR4/NF- $\kappa$ B pathway. This step is termed “priming” and causes a transcriptional up-regulation of the transcription of *nlrp3* mRNA and for *pro-il-1 $\beta$*  and *-il-18* (Latz et al. 2013) (Fig. 2). In a second step, intracellular sensing of specific ligands (DAMPs) leads to the recruitment and oligomerization of the key adaptor protein, ASC, which, through its a Caspase activation and recruitment domain (CARD) facilitates the subsequent recruitment and activation of Caspase-1. In a final activating step this protease catalyses the proteolytic cleavage of inactive pro-IL-1 $\beta$  or pro-IL-18 proteins into secreted bioactive cytokines which initiate a plethora of potent inflammatory responses. Furthermore, activation of Caspase-1 induces Gasdermin-D-mediated pyroptosis, a form of cell death frequently observed during invasion by gram-negative and gram-positive pathogens (Fig. 2).

In addition to canonical inflammasomes comprising NLRP3, ASC and Caspase-1, recent studies have identified an alternative non-canonical NLRP3 inflammasome which consists of Caspase-11 (Caspase-4 and Caspase-5 in human) and not Caspase-1. The non-canonical pathway is seen in infections with gram-negative bacteria, where Caspase-11 binds directly to cytosolic LPS. This promotes inflammasome-independent pyroptosis and the assembly of the NLRP3 inflammasome and activation of Caspase-1 to cleave pro-IL-1 $\beta$  and pro-IL-18 into secreted bioactive cytokines (Kayagaki et al. 2011; Rathinam et al. 2012) (Fig. 2).

IL-1 $\beta$  and IL-18 are important pro-inflammatory mediators of the mucosal inflammatory response. The presence of



**Fig. 2** Canonical and non-canonical activation of NLRP3. The canonical pathway needs two signals to initiate NLRP3 inflammasome activation. Signal 1 is also termed priming and is triggered by pathogen-associated molecular patterns (PAMPs) from extra cellular environment. Signal 1 upregulates the availability of NLRP3 protein, pro-IL-18 and -IL-1 $\beta$  via NF- $\kappa$ B mediated transcription. Signal 2 is activated by intracellular danger-associated molecular patterns (DAMPs) of the host. This leads to oligomerization of NLRP3

proteins and to a recruitment of ASC and Caspase-1 thus completing the NLRP3 inflammasomes assembly and activation. Activated NLRP3 inflammasomes will cleave pro-IL-18 and -IL-1 $\beta$  precursor cytokines into bioactive IL-18 and IL-1 $\beta$  and initiate the inflammatory response. The non-canonical pathway does not requires signal 1 or priming but is activated by intracellular DAMPs such as ROS. Upon activation its activity follows the canonical activation pathway

IL-1 $\beta$  can induce various cellular activities, including the proliferation, differentiation and apoptosis of both immune and non-immune cells (Huber et al. 2012; Vela et al. 2002). Additionally, IL-1 $\beta$  can co-stimulate IL-6 production which acts as a growth factor for B cell proliferation and initiate the release of other pro-inflammatory cytokines such as TNF- $\alpha$ , IL-23 (and IL-6) that can polarise the adaptive immune response to a Th2 or a Th17 response depending on the antigenic environment (Dinarello 2009).

The importance of IL-1 $\beta$  in the pathogenesis of colitis has been well established (Ning et al. 2015). In addition, numerous studies have revealed that secretion of IL-1 $\beta$  is elevated in the sera of patients with IBD (Sartor 1994) and mice subjected to DSS-induced colitis (Bauer et al. 2010).

Importantly inhibition of IL-1 $\beta$  has shown to alleviate DSS-induced colitis (Siegmond 2002).

Other studies have indicated that in contrast to IL-1 $\beta$ , IL-18 plays a major role in suppressing colitis and CAC. Polymorphisms of the *il-18* gene have confirmed a strong association of this cytokine with an increased susceptibility to CD (Tamura et al. 2002). This suggests that IL-18 signalling provides protection against a development of intestinal inflammation. Mice deficient for IL-18 and IL-18 receptor were hyper-susceptible to DSS-induced colitis, which was associated with higher mortality rates and more severe histopathological changes (Takagi et al. 2003). In a similar study, IL-18 $^{-/-}$  and IL18r $^{-/-}$  mice also developed severe DSS-induced colitis with high lethality and more histopathological abnormalities and were more

susceptible to AOM/DSS-induced colon tumorigenesis as compared to WT mice, suggesting an essential and protective role of IL-18 signalling in colorectal cancer (Salcedo et al. 2010). MyD88 KO mice, which are defective in both IL-1 $\beta$  and IL-18 production and the downstream signalling of their respective receptors, showed increased colonic epithelial proliferation and colorectal tumorigenesis (Salcedo et al. 2010). The explanation proposed was that the increase in tumorigenesis was caused by a decrease in DNA damage response genes causing insufficient response to DNA damage. Additionally, IL-18 is a key mediator in epithelial regeneration by the up-regulation of adhesion molecules (Stuyt et al. 2003) during the early stages of colitis (Allen et al. 2010; Hirota et al. 2011; Nowarski et al. 2015; Zaki et al. 2010a). Besides its indirect tumour-suppressive role in CAC, IL-18 has been associated with a T helper 1-skewed immune-stimulatory, anti-tumorigenic response through its ability to induce IFN- $\gamma$  (Okamura et al. 1995) and its effects on enhancing the cytosolic activity of cytotoxic T cells and NK cell response (Chaix et al. 2008; Novick et al. 2013; Takeda et al. 1998). Furthermore, high levels of IL-18 have been detected in lamina propria mononuclear cells (LPMCs) and colon epithelial cells of patients with Crohn's disease (Monteleone et al. 1999; Pizarro et al. 1999).

In an experimental T cell-mediated colitis model administration of a recombinant IL-18 antisense-expressing adenoviruses was able to reduce IL-18 and suppress IFN- $\gamma$  thus ameliorating colitis in vivo (Wirtz et al. 2002). The connection between IL-18 and IFN- $\gamma$  was supported by an analysis of LPMCs from IL-18<sup>-/-</sup> mice which featured an exacerbated form of DSS colitis and produced a significantly higher amount of IFN- $\gamma$  (Takagi et al. 2003). Furthermore, the in murine colitis models neutralisation of IL-18 has shown to ameliorate intestinal inflammation (Siegmond et al. 2001a; Sivakumar et al. 2002) and may therefore an interesting candidate for a targeted immunotherapy of human intestinal inflammatory diseases. These experiments have highlighted the dual role of IL-18 in intestinal homeostasis and

colitis. Early in the mucosal immune response, its expression by IECs and LPMCs indicates a protective, local role through epithelial regeneration and proliferation in response to injury. In chronic inflammation its excessive production can enhance inflammation, which potentially promotes tumorigenesis and tumour growth (Reuter and Pizarro 2004).

### The role of NLRP3 in colitis-associated and colitis-associated cancer: lessons from mouse models

NLRP3 inflammasome and its activation in intestinal pathologies have been investigated predominantly using mouse models of chemically induced intestinal inflammation and CAC specifically the 2,4,6-trinitrobenzene sulphonic acid (TNBS) and the dextran sulphate sodium (DSS) models of inflammation, and the azoxymethane (AOM or AOM/DSS) model of CAC induction respectively (Table 2).

In murine of TNBS models the chemical compound is administered intrarectally and mediates a T cell-mediated immune response, similar to chronic colonic inflammation as described in CD (Wirtz and Neurath 2007). In the DSS colitis model, DSS is dissolved in the drinking water and is ingested. The chemical causes significant damage to the epithelial barrier by causing acute colonic crypt destruction and mucosal ulceration. The compromised epithelial barrier is invaded by gut microflora which enters to the lamina propria resulting in massive infiltration of inflammatory cells and up-regulation of pro-inflammatory cytokines comparable to human ulcerative colitis (Chassaing et al. 2014; Ni et al. 1996). Administering DSS in weekly cycles alternating it with water results in a condition that is similar to clinically observed conditions of active and remission phases of UC. Finally, AOM a potent genotoxic carcinogen that causes DNA damage in

**Table 2** Examples of colitis and CAC mouse models

Mouse model	Trigger	Role of NLRP3	References
NLRP3 <sup>-/-</sup>	DSS/TNBS	Protective	Zaki et al. (2010a)
NLRP3 <sup>-/-</sup>	DSS	Protective	Allen et al. (2010)
NLRP3 <sup>-/-</sup>	DSS	Protective	Hirota et al. (2011)
NLRP3 <sup>-/-</sup>	DSS	Harmful	Bauer et al. (2010)
NLRP3 <sup>-/-</sup>	DSS	Harmful	Elinav et al. (2011)
NLRP3 <sup>-/-</sup>	Oxazolone	Protective	Itani et al. (2016)
Nlrp3 <sup>R258W</sup> × Rag1 <sup>-/-</sup>	Spontaneous	Protective	Yao et al. (2017)
NLRP3 <sup>-/-</sup>	AOM/DSS	Protective	Allen et al. (2010), Zaki et al. (2010b)
NLRP3 <sup>-/-</sup>	AOM/DSS	None	Hu et al. (2011)
Nlrp3 <sup>R258W</sup>	AOM/DSS	Protective	Yao et al. (2017)



epithelial cells is used in combination with repeated DSS administration. The resulting chronic inflammation promotes the development of colorectal cancer in cells carrying mutations generated by AOM (Tanaka et al. 2003).

The role of NLRP3 in colitis and CAC is still controversial with some studies showing a protective role while other studies demonstrate a detrimental effect of NLRP3 activation (Fig. 2; Table 2). Studies of individual inflammasome components in colitis models before the inflammasome was identified as complex molecular platform questioned the role of Caspase-1 (Dupaul-Chicoine et al. 2010; Siegmund et al. 2001b). The phenotype of Caspase-1<sup>-/-</sup> DSS colitis mice showed reduced acute and chronic colitis (Siegmund et al. 2001b). Both Caspase-1<sup>-/-</sup> and ASC<sup>-/-</sup> mice showed an increased susceptibility to DSS colitis and disease severity was linked to reduced IL-18 production. Conversely, the administration of exogenous IL-18 completely reversed severity of colitis (Dupaul-Chicoine et al. 2010). Intestinal epithelial cells rather than lamina propria cells were shown to be the source of IL-18 that was needed for early induction of tissue repair and epithelial cell regeneration.

The discrepancy in the above studies was explained by the novel discovery of two confounding aspects of the Caspase-1<sup>-/-</sup> mouse model. First, Caspase-1<sup>-/-</sup> mice additionally lacked Caspase-11 (Kayagaki et al. 2011). Therefore all results based on previous studies of this mouse model during DSS colitis is complicated by the contribution of Caspase-11 to disease pathogenesis.

The second controversy revolves around the fact that the Caspase-1<sup>-/-</sup> Caspase-11<sub>129mt/129mt</sub> mice harbour colitogenic microbiota that have shown to enhance the severity of DSS colitis (Elinav et al. 2011). A recent study characterised the intrinsic functions of Caspase-1 in vivo. The study generated Caspase-1<sup>-/-</sup> and Caspase-11<sup>-/-</sup> mice on a pure C57BL/6N genetic background with a non-dysbiotic intestinal microbiota. Using these gut microbiota it could be shown that that canonical Caspase-1 activation, not Caspase-11, is responsible for exacerbating DSS-induced colitis (Blazejewski et al. 2017).

The protective role of NLRP3 in colitis was suggested by experiments that showed enhanced colitis in NLRP3<sup>-/-</sup> mice mediated by a loss of epithelial barrier integrity and reduction of IL-18 (Zaki et al. 2010a), defective antimicrobial mechanism leading to bacterial dysbiosis and increased susceptibility to DSS- and TNBS-induced colitis (Hirota et al. 2011).

The role of the NLRP3 inflammasome in the pathogenesis of UC was analysed in an oxazolone-induced murine colitis model. Intrarectal delivery of oxazolone (OXA) created a relevant UC pathogenesis model mediated by Th2 cytokines. In this model a reduction of mature IL-1 $\beta$  and IL-18 production induced a higher severity of colitis in OXA-treated NLRP3<sup>-/-</sup> mice when compared to WT mice. Conversely

this increase in severity could be prevented by exogenous administration of IL-1 $\beta$  or IL-18. This study shows that NLRP3 inflammasome-derived IL-1 $\beta$  and IL-18 may play a protective role against OXA-induced colitis (Itani et al. 2016).

Controversially, competing studies showed that DSS-induced colitis was attenuated in NLRP3<sup>-/-</sup> mice potentially mediated by a local reduction of pro-inflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$  and IFN- $\gamma$  (Bauer et al. 2010). Exposure to DSS and concurrent treatment with the Caspase-1 inhibitor Pralnacasan ameliorated colitis (Bauer et al. 2007). An attenuation of colitis in NLRP3-deficient mice has been confirmed by others supporting the function of NLRP3 as a negative regulator of the inflammatory process (Elinav et al. 2011).

Genetic models of NLRP3<sup>-/-</sup>, Caspase-1<sup>-/-</sup> and ASC<sup>-/-</sup> mice exposed to AOM/DSS have an increased tumour burden (Allen et al. 2010). Using bone marrow chimaeras, it was demonstrated that tumorigenesis suppressive signalling by NLRP3 was located in the haematopoietic and not in the epithelial compartment. This correlated colitis-associated tumours with a defective production of IL-18 during the initiation of inflammation in the AOM/DSS model. Consequently, the role of NLRP3 in CAC has mainly been reported as a negative regulator in colitis-associated tumorigenesis (Allen et al. 2010; Zaki et al. 2010b).

Consistent with a protective role of NLRP3 in tumorigenesis NLRP3<sup>-/-</sup> mice were highly susceptible to AOM/DSS-induced inflammation and the treatment caused increased tumours in the colon. The mechanism proposed was that NLRP3-dependent IL-18 secretion is required for STAT1 activation and IFN- $\gamma$  induction leading to decreased immune tumour surveillance in the absence of IL-18. This phenotype was reduced with administration of recombinant IL-18 (Zaki et al. 2010b).

The ability of NLRP3 to release bioactive IL18 is a potential mechanism explaining the protective role of this cytokine against CAC development. However, another study found no difference in CAC between NLRP3-deficient and WT mice in a AOM/DSS model (Hu et al. 2011). The reason for these discrepancies observed in the Nlrp3<sup>-/-</sup> colitis or CAC model phenotype is not clear, but could be due to differences in length and concentration of DSS treatment or to baseline differences in the composition of the intestinal microbiota in experimental mouse colitis.

Human and murine studies suggest that bacterial dysbiosis promotes inflammation in human and mouse colitis and CAC models (Kitajima et al. 2001; Richard et al. 2018). Studies in mice deficient in inflammasome genes have provided evidence that specific inflammasomes like NLRP6 and NLRP3 are major regulators of commensal microbiota. A study in *Nlrp3*<sup>-/-</sup> mice suggested that the NLRP6/ASC

inflammasome acts as a crucial regulator of the gut microbiota (Elinav et al. 2011). Another study that observed a significant increase in bacterial counts in stool, colon, mesenteric lymph node and liver in DSS colitis of *Nlrp3*<sup>-/-</sup> mice compared to DSS colitis in wild-type mice demonstrated that NLRP3 plays a role in controlling commensal overgrowth and bacteraemia (Zaki et al. 2010a).

How NLRP3 regulates the microbial composition in the intestines is not clear. This question was addressed by comparing faecal microbiota of *Nlrp3*<sup>-/-</sup> deficient mice to their WT littermates (Hirota et al. 2011). Only NLRP3<sup>-/-</sup> mice were shown to carry a specific bacterial composition with potentially pathogenic members of the family Enterobacteriaceae including the species *Citrobacter*, *Proteus* and *Shigella* (Hirota et al. 2011). Furthermore, the unique genera *Mycobacterium*, *Collinsella*, *Clostridium* and *Ralstonia* were identified which were not detectable in WT littermates. Additionally, it could be shown that colon crypt secretions obtained from NLRP3<sup>-/-</sup> mice ex vivo had decreased bactericidal activity against *E. coli*. The significant difference in composition of the intestinal microbiota in the NLRP3<sup>-/-</sup> mice could explain the increased susceptibility to DSS- and TNBS-induced colitis (Hirota et al. 2011).

Further studies have demonstrated that the distinct commensal bacterial species *Proteus mirabilis* induces a robust IL-1 $\beta$  secretion via NLRP3 inflammasome activation in newly recruited intestinal Ly6C<sup>high</sup> monocytes during DSS colitis. This could be linked to an increased severity of disease (Seo et al. 2015). However, the molecular pathways by which intestinal bacterial populations in NLRP3 inflammasome-deficient mice promote intestinal inflammation are still elusive. It has been speculated that this could be due to their ability to upregulate the generation of pro-inflammatory chemokines and cytokines such as CCL5 (Elinav et al. 2011), IL-6 and TNF- $\alpha$  (Hu et al. 2013).

NLRP3<sup>-/-</sup> mice show a more severe colitis when compared to WT mice after infection with the intestinal pathogen *Citrobacter rodentium* (Song-Zhao et al. 2013). This could be due to a lack of downstream cytokines IL-1 $\beta$  and IL-18 in the gene-deficient mice and allows the conclusion that activation of the NLRP3 inflammasome is necessary for an attenuation of *Citrobacter rodentium* driven intestinal inflammation.

In contrast to gene-deficient models, the NLRP3<sup>R258W</sup> mouse model displays an enhanced NLRP3 inflammasome signalling. These mice develop an auto-inflammatory response in the skin (Meng et al. 2009). In the intestine they maintain homeostasis and remain strongly resistant to experimental colitis and subsequently, colorectal cancer. This is due to a distinct microbiota in NLRP3<sup>R258W</sup> mice with an increased presence of bacterial species such as *Clostridium XlVa* and *Lactobacillus murinus* and also a significant reduction of colitogenic bacteria such as *Akkermensia muciniphila*

which promote the local differentiation of T<sub>regs</sub>, that contribute to homeostasis in the gut (Yao et al. 2017). Further work needs to be done to elucidate the signalling pathways by which resident bacteria stimulate the NLRP3 inflammasome to induce colitis in IBD.

## Diet, microbiota and the activation of NLRP3: bowel cancer as an end stage of inflammation

Environmental factors, together with the individual genetic make-up and the innate immune response play role in development of IBD (Marion-Letellier et al. 2016). Two central environmental factors are diet and the composition of symbiotic microorganisms that live in our gastrointestinal tract (GI), the so-called microbiome. Microbiota composition has been shown to modulate metabolism-associated conditions like obesity and inflammatory diseases of the bowel like IBD and associated cancers such as CAC and CRC (Requena et al. 2018). A healthy diet helps to maintain a balanced and healthy microbiota and consequently, immune homeostasis in the gut. Unbalanced consumption of nutrients can lead to a dysbiosis of the microbiota and inflammation (Geuking et al. 2014; Marion-Letellier et al. 2016). Chronic insults from dietary metabolites activate NLRP3 and IL-1 $\beta$  production and thus progress disease pathogenesis (Camell et al. 2015). Consequently, diet has been identified as an important driver of the development a large percentage (50–90%) of tumours of the bowel (Kasdagly et al. 2014). For example, diet rich in fat increases the amount of bile acid which consists to 58% of deoxycholic acid (DCA). DCA has been found to disrupt epithelial integrity due to Cathepsin B activation of NLRP3 and leads to barrier disruption observed in DSS-induced colitis. In mice deficient for NLRP3 or Caspase 1 DSS-induced colitis could not be established which underlines the role of NLRP3 in the development of colitis in a high fat environment (Zhao et al. 2016). Another chronic insult by the ingested diet is the presence of dietary cholesterol in the intestines. In an AOM-treated mouse model this has been associated with a hyperactivity of NLRP3 resulting in an increase in IL-1 $\beta$  (Du et al. 2016). In general, saturated lipids, ceramide (Vandanmagsar et al. 2011) and uric acid can act as DAMPs that induce unwanted NLRP3 activation by initiating the production of ROS (Camell et al. 2015). On the other hand, some metabolites like omega-fatty acids prevent activation of NLRP3 and thus have an anti-inflammatory effect (Yan et al. 2013). These examples allow an insight how inflammation, colitis and CAC can be supported by various dietary parameters.

Under normal physiological conditions the symbiotic microbiota support the host by breaking down complex polysaccharides in dietary fibre into short chain fatty acids

(SCFA) with less than six carbon atoms (Nieuwdorp et al. 2014). The predominant forms are acetate (C2), propionate (C3) and butyrate (C4). SCFA are the major products of bacterial fermentation and important as energy source for colonic epithelial cells (Huycke and Gaskins 2004). SCFA induce a favourable intestinal environment in a variety of ways and high fibre diet boosts bacterial species which produce SCFA (Desai et al. 2016; Kelly et al. 2015). The presence of dietary fibre and SCFA also protects in DSS directly through activation of NLRP3 possibly in colonic epithelial cells (Macia et al. 2015). While the molecular pathways of this interaction are still elusive it demonstrates the important role of diet in intestinal homeostasis.

Furthermore, butyrate as one of the main SCFA induces functional Tregs via intrinsic up-regulation of the *Foxp3* gene (Furusawa et al. 2013). The extrathymic differentiation of T<sub>regs</sub> in the periphery is enhanced via the conserved non-coding sequence 1 (CNS-1)-dependent pathway in the presence of butyrate and propionate (Arpaia et al. 2013). Butyrate activates the intestinal butyrate GPR109A receptor which drives the differentiation of T<sub>regs</sub> and modulates immune responses by up-regulation of the production of IL-10, suppressing colonic inflammation and carcinogenesis in a mouse model of intestinal inflammation associated with CAC (Singh et al. 2014). Increased T<sub>reg</sub> initiate an anti-inflammatory

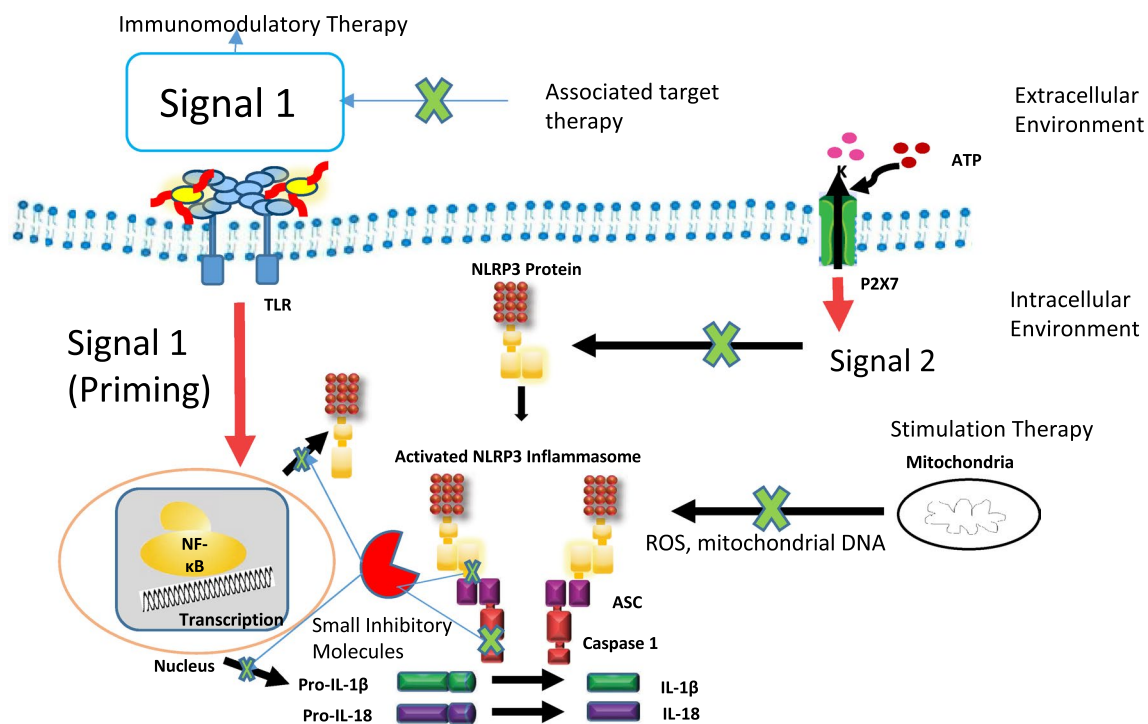
response and act as antagonist to NLRP3 thus maintaining the homeostasis in experimental colitis and CAC (Yao et al. 2017).

## Future directions of CAC therapy by intervention with NLRP3 activation

An improved understanding of the mechanistic interactions between diet and microbiota, and inflammasomes such as NLRP3 will reveal new potential therapies that target these pathways (Fig. 3). Here we outline some opportunities for interventions (Table 3).

### Diet/metabolic immunomodulators

Metabolite targeted therapy can be used to modulate the hyper activation/blockage of NLRP3. Metabolic product-induced inflammatory mediators like plasminogen activator inhibitor (PA)-1, sphingosine-1-phosphate and ceramide-1-phosphate constitute a link that allows modulation of NLRP3 activity. Targeting these mediators results in a therapy of colitis. Lipoxygenase is needed to recruit monosodium urate which activates NLRP3 in gout. This mechanism needs to be investigated in colitis and CAC models (Amaral et al. 2012). A further interesting possibility is the inhibition



**Fig. 3** Different therapeutic interventions targeting NLRP3 assembly or activation. Small molecule inhibitors modify or prevent NLRP3 assembly. Associated target therapy targets NLRP3 activation through

changes in diet and microbiota, or modulation of macrophages. Therapy against novel stimulation of NLRP3 such as activation by mitochondria



**Table 3** Opportunities for interventions with colitis and CAC

Potential NLRP3-mediated interventions to treat colitis and CAC	Therapeutic approach
Immunomodulators	Various dietary molecules which can help to reduce only detrimental activity of NLRP3
Stimulation therapy	Targeting the various activating mechanism of NLRP3
Inhibitory molecules	Designing inhibitory small molecules against activation, assembly or various subunits of NLRP3
Associated target therapy	Chemokines, cytokines, signalling cascade and immune cells like macrophage's which support in negative activity of NLRP3

of ceramide synthesis by increasing fatty acid oxidation to reduce fatty acid inflammation (Schilling et al. 2013).

### Inhibition of de novo activation of NLRP3

The cytoskeleton protein  $\alpha$ -microtubulin is an activator of NLRP3. This protein supports NLRP3 assembly by recruiting ASC from mitochondria. This supporting role of NLRP3 activation requires an assistance from dynein (Akira et al. 2013). The microtubules have to undergo post-translational modification by acetylation by the Mec17 gene product in order to activate NLRP3 (Akira et al. 2013). An activation of the enzyme SIRT2 which is  $\alpha$ -tubulin deacetylase is required by DAMPs in order to activate NLRP3. A targeted therapy against this mechanism of NLRP3 assembly could offer an interesting treatment opportunity.

### Small molecule targeted therapy

Novel small molecule specific inhibitors such as MCC950, CY-09, BHB has been used to pharmacologically target NLRP3 activation and successfully treat a variety of inflammatory disorders (Coll et al. 2015; Jiang et al. 2017; Youm et al. 2015). These inhibitory molecules target various protein components such as ASC or Caspase-1 or inhibit production of NLRP3-mediated effector cytokines such as IL-1 $\beta$  (Mangan et al. 2018). At present there are no specific NLRP3 inhibitors used in clinical IBD therapy. However a few compounds that show inhibition of NLRP3 activity have emerged as potential therapeutics for IBD (Perera et al. 2017). Most of these are nonspecific with unknown mechanisms, limiting their progression to clinical usage for long term application in chronic IBD but specific NLRP3 inhibitors have shown promise in IBD patient tissues and colitis mouse models. A recent study using specific inhibitor MCC950 in the spontaneous chronic IBD mouse model Winnie, illustrated the potent therapeutic effect of NLRP3 blockade. Established colitis was ameliorated by a 3 week treatment of orally administered MCC950 (Perera et al. 2018). Another study used Glyburide alleviating colitis and preventing disease onset in IL10<sup>-/-</sup> mice. This drug also inhibited pro-inflammatory

cytokines in mucosal explants from Crohn's patients (Liu et al. 2016). Furthermore, the benzimidazole-containing synthetic small molecule inhibitor Fc11a-2 alleviated colitis in a DSS-induced colitis mouse model (Liu et al. 2013). In this study the mechanism of action was found to be inhibition of cleavage of pro-Caspase-1 following a reduction in production of IL-1 $\beta$  and IL-18 suppressing the activation of NLRP3 inflammasome. Finally, a non-cytotoxic, novel acrylate derivative inhibitor INF39 which does not block Caspase 1. Oral administration of INF39 in a TNBS-induced rat colitis model attenuated intestinal inflammation (Cocco et al. 2017). The use of small molecule inflammasome inhibitors also shows promise when it comes to prevention of CAC. A study on the small molecule andrographolide (Andro) shows that it is protective against AOM/DSS induced colon carcinogenesis in mice by inducing mitophagy in macrophages which leads to a reversed mitochondrial membrane potential collapse that inactivates the NLRP3 inflammasome and prevents the development of CAC (Guo et al. 2014). A further example is the small-molecule AMPK activator GL-V9 which resolves colitis and is protective against tumorigenesis in colitis-associated colorectal cancer. GL-V9 acts by triggering autophagy in cells leading to activation of the NLRP3 inflammasome (Zhao et al. 2018). In summary the regulation of chronic inflammation in the intestines through pharmacological intervention of small molecule NLRP3 inhibitors in IBD patients could be a potential therapeutic option for preventing CAC.

### Combination therapy

Combination of small molecule therapy along with diet modulators could be tried to increase effectiveness. For example various combinations of diet modulators can be used such as 5-aminosalicylic acid together with fish oil. This combination lowered the inflammatory score compared to treatment with 5-aminosalicylic acid alone in rats with TNBS-induced colitis (Mbodji et al. 2013). In human tissues the combination of glutamine and arginine have been shown to reduce TNF- $\alpha$  production in colonic biopsies of colitis patients (Lecleire et al. 2008).

## Conclusion

There is clear evidence supporting the NLRP3 inflammasome as key player in the inflammatory response in colitis (Schoultz et al. 2009; Villani et al. 2009) with ultimate implications for CAC development (Allen et al. 2010). However, it is also clear from the conflicting evidence outlined in this review that involvement of the NLRP3 inflammasome in inflammatory processes leading to tumour development is complex and may be context dependent. Therefore carefully designed follow up experiments are warranted, where conditions for the induction of colitis including controlled intestinal microbiota, are carefully controlled. Unravelling the role of the NLRP3 inflammasome in intestinal inflammation will provide insights for the role of NLRP3 in intestinal epithelial cells and the pathways employed by the mucosal immune system to modulate the microbiota and integrate with the adaptive immune response to defend the integrity of the gut mucosa. Understanding the mechanisms that underpin these interactions also more broadly builds on the current strong interest in understanding the immune pathways underpinning chronic inflammation in tumourigenesis.

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## Compliance with ethical standards

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

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