Innate immunity comprises several inflammation-related modulatory pathways which receive signals from an array of membrane-bound and cytoplasmic pattern recognition receptors (PRRs). The NLRs (NACHT (NAIP (neuronal apoptosis inhibitor protein), C2TA (MHC class 2 transcription activator), HET-E (incompatibility locus protein from Podospora anserina) and TP1 (telomerase-associated protein) and Leucine-Rich Repeat (LRR) domain containing proteins) relate to a large family of cytosolic innate receptors, involved in detection of intracellular pathogens and endogenous byproducts of tissue injury. These receptors may recognize pathogen-associated molecular patterns (PAMPs) and/or danger-associated molecular patterns (DAMPs), activating host responses against pathogen infection and cellular stress. NLR-driven downstream signals trigger a number of signaling circuitries, which may either initiate the formation of inflammasomes and/or activate nuclear factor \( \kappa B \) (NF-\( \kappa B \)), stress kinases, interferon response factors (IRFs), inflammatory caspases and autophagy. Disruption of those signals may lead to a number of pro-inflammatory conditions, eventually promoting the onset of human malignancies. In this review, we describe the structures and functions of the most well-defined NLR proteins and highlight their association and biological impact on a diverse number of cancers.

NOD-like receptors

The innate immune system is our first line of defense against infections from an enormous diversity of microbes and viruses. The human innate immunity relies on a wide range of receptors and complex downstream networks which respond against infectious pathogens. Activation of these immune pathways leads to a broad range of pro- and/or anti-inflammatory signals, including the secretion of interferons, tumor necrosis factors and cytokines [1]. Disruption in the balance of these signals may lead to chronic inflammatory states and directly affect cellular processes, such as cell cycle progression and apoptosis, creating a background context for the rise of maladies, such as cancer [1,2].

In humans, innate immune receptors are classified into several families [3]. Amongst the most well-characterized receptors are the TLRs (Toll-like Receptors) and NOD-like receptors (NLRs) [NACHT (NAIP (neuronal apoptosis inhibitor protein), C2TA (MHC class 2 transcription activator), HET-E (incompatibility locus protein from Podospora anserina) and TP1 (telomerase-associated protein), and Leucine-Rich Repeat (LRR) domain containing proteins] [4–6]. While TLRs act as surface receptors found in cell and organelle (endosome) membranes, the NLRs are cytosolic receptors involved in the detection of intracellular pathogens and endogenous byproducts of tissue injury [7]. The NLRs are also known as a subgroup of pattern recognition receptors (PRRs), which act as innate immunity ‘sensors’ of pathogen-associated
molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [8,9]. Typically, the PAMPs recognized by NLRs are bacterial cell-wall derivates [10], microbial toxins [11], viruses [12] or even whole pathogenic microbial organisms [13]. The DAMPs are host-derived molecules released by injured cells, including extracellular ATP [14], hyaluronan [15] and monosodium urate (MSU) [16]. Therefore, NLRs act as key activators of innate immune responses which, upon detection of cell damage and infections, may lead to the expression and/or activation of stress kinases, interferon response factors (IRFs) and inflammatory caspases [17–21].

**NLR protein structure and subfamilies**

A number of NLR homologs have been described in both vertebrate and invertebrate species [22]. In humans, the NLR protein family comprises 22 members [23–25]. All NLR proteins share a typical architecture, including: (i) a centrally located nucleotide-binding NACHT domain, which mediates self-oligomerization and is essential for ATP-dependent NLR activation; (ii) an N-terminal effector domain, which interacts with adaptor molecules and downstream effectors to mediate signal transduction; and (iii) a C-terminal region, comprising variable numbers of LRR domains, involved in the recognition of molecular patterns (Figure 1) [4]. Specifically, human NLRs are divided into four subfamilies, according to the nature of their N-terminal regions. These regions may contain (i) an acidic transactivation domain (AD) (NLRA subfamily), (ii) a baculoviral inhibitory repeat-like domain (BIR) (NLRB subfamily), (iii) a caspase activation and recruitment domain (CARD) (NLR subfamily) or (iv) a pyrin domain (PYD) (NLRP subfamily) (Figure 1) [1,4,8,17,21,24].

The NLA subfamily comprises a sole member, namely: the Class II Major Histocompatibility Complex Transactivator (CIITA). Apart from the AD domain, CIITA displays four LRRs and a GTP binding domain (Figure 1). GTP binding facilitates the protein transport into the nucleus, where it acts as a positive regulator of class II major histocompatibility complex gene transcription (Figure 2) [26]. In this case, transcriptional activation is not achieved through DNA binding, but via an intrinsic acetyltransferase (AT) activity [27,28]. Similarly, the NLRB subfamily comprises only one member, namely, the NLR Family Apoptosis Inhibitory Protein (NAIP). NAIP is an anti-apoptotic protein which acts by inhibiting (i) the activities of Caspase (CASP) 3 (CASP3), CASP7 and CASP9 [29], (ii) the autolysis of pro-CASP9 and (iii) the cleavage of pro-CASP3 by CASP9 [30]. NAIP is a mediator of neuronal survival in several pathological conditions, preventing apoptosis induced by a variety of signals [31].

NLR is the second largest subfamily of NLRs, consisting of six members: nucleotide oligomerization domain 1 (NOD1) (NLRC1), nucleotide oligomerization domain 2 (NOD2) (NLRC2), NLRC3, NLRC4, NLRC5, and NLRC11. The NLRC3, NLRC5 and NLRC11 members are classified in the NLR subfamily due to their homology and phylogenetic relationships, although their N-terminal domains have not been fully characterized yet [32]. NOD1 and NOD2 (Nucleotide-Binding Oligomerization Domain-Containing Proteins 1 and 2) are considered as the founding NLRs as well as the two major members of the NLR subfamily [33]. NOD1 and NOD2 recognize intracellular bacterial components, which enter the cell either via direct bacterial invasion or by other cellular uptake mechanisms [34,35]. NOD1 and NOD2 contain, respectively, one and two N-terminal oligomerization CARD domains and detect distinct motifs of peptidoglycans (PGNs) [36,37]. NOD1 recognizes d-γ-glutamyl-meso-DAP (L-Ala-γ-d-Glu-meso-diaminopimelic acid) (IE-DAP (d-γ-glutamyl-meso-DAP)) dipeptides, which are found in PGNs from all Gram-negative and some Gram-positive bacteria, while NOD2 recognizes the muramyl dipeptide (MDP) structure found in almost all bacterial types [33,36–38]. Therefore, NOD2 acts as a broader sensor of bacterial infection, while NOD1 recognizes a more specific subset of bacterial strains.

The NLRP subfamily of receptors consist of 14 members, characterized by the presence of an N-terminal pyrin (PYD) effector domain [39] which possesses a conserved sequence motif found in more than 20 human proteins, with functions in apoptotic and inflammatory signaling [8,39]. Within this subfamily, at least six receptors (NLRP1, NLRP3, NLRP6, NLRP7, NLRP12, NLRC4) have been reported to operate through formation of inflammasome complexes [39]. These NLRPs recognize various ligands originated from microbial pathogens (PGN, flagellin, viral RNA, fungal hyphae etc.), host cells (cholesterol crystals, uric acid etc.), and environmental sources (alum, asbestos, silica, alloy particles, UV radiation, skin irritants etc.) [8]. Studies have shown that NLRP genes play important roles in both the innate immune system and mammalian reproduction [8,40], suggesting that NLRPs might play a role in oogenesis and early preimplantation embryogenesis [8,40].

**NLR signaling and inflammasome-related pathways**

NLR activation is translated through distinct subpathways to achieve pro- or anti-inflammatory responses (Figure 2). The downstream signals involved are modulated by the type of ligands bound to the NLR and may also depend on the cellular context. For instance, NOD1 and NOD2 receptors bind to the membrane of early endosomes in the cytoplasm,
Figure 1. Protein structure representation of each NLR subfamily
Respective domains are indicated as follows: **CARD**: Caspase recruitment domain; **AD**: Acidic transactivation domain; **NACHT**: NAIP (neuronal apoptosis inhibitor protein), C2TA (MHC class 2 transcription activator), HET-E (incompatibility locus protein from *Podospora anserina*) and TP1 (telomerase-associated protein); **BIR**: Baculoviral inhibitory repeat-like domain; **X**: Unknown; **PYD**: Pyrin domain. Green open circles represent **LRR** (Leucine-rich repeat).

specifically interacting with the actin cytoskeleton in order to maintain an inactive state [41,42]. PGNs that are transported through the membrane [43–48] are promptly recognized by these NOD receptors. Ligand-bound NOD1 and NOD2 self-oligomerize through CARD–CARD interactions, using the endosomal membrane as a scaffold for the assembly of signaling complexes [46,49]. Oligomerized NODs send signals via the serine/threonine receptor-interacting protein 2 (RIP2) kinase [50], which, in turn, mediates ubiquitination of the nuclear factor κB (NF-κB) essential modulator (NEMO)/IKKγ complex and, consequently, activation of NF-κB and production of inflammatory cytokines [4,51,52]. Furthermore, poly-ubiquitinated RIP2 also recruits TAB (TGF-β-activated kinase 1 and MAP3K7-binding protein) and its associated kinase TAK1 (TGF-β-activated kinase 1) [53,54]. TAK1 is a downstream activator of stress kinase, mitogen-activated protein kinase (MAPK) cascades, which activate JNK (c-Jun N-terminal kinase) and p38 MAPK toward activator protein 1 (AP-1) transcriptional activity [38,55,56].

Both NOD1 and NOD2 also activate the host response through an alternate pathway, independent of RIPK2 and NF-κB signaling [21]. These receptors can detect intracellular bacteria which cross the plasma membrane and then recruit the autophagic essential adapter protein ATG16L1 to the bacterial entry site, promoting highly specific
lysosome-mediated degradation of the invading microbe by the autophagic machinery [21,57–59]. In addition to detecting bacterial components, NOD1 and NOD2 receptors also monitor the cytoplasmic environment, responding to cytoskeleton perturbations and ER stress [60,61], which, ultimately, activate autophagy [62–64] and NF-κB-driven inflammation [61,65,66]. This effect allows these NOD receptors to respond to pathogens that do not produce specific PGNs [67].

**Inflammasome-forming NLRs**

The inflammasome is a multiprotein intracellular complex, which is frequently formed in response to several pathophysiological stimuli [67]. Despite its cytosolic localization, inflammasome structures are capable of launching an effective immune response against bacteria, fungi and viruses [68]. Indeed, inflammasome activation is an essential component of the innate response, playing a critical role in clearance of pathogenic insults and/or damaged cells [69].

In brief, the inflammasome structure includes: a sensor (NLR), an adaptor protein (ASC (apoptosis-associated speck-like protein containing CARD)) and an effector molecule (pro-CASP1) [70]. ASC is a bipartite protein consisting of a PYD and a caspase recruitment domain (CARD) [39,71]. In resting cells, caspase-1 is present in a catalytically inactive pro-form (zymogen) called pro-caspase-1 [72]. Caspases have long been established as executioners of the apoptotic response, also contributing to inflammasome activation [69].
The inflammasome activation initiates through the auto-coactivation of caspase-1, resulting in cleavage of pro-interleukin-1β (pro-IL-1β) and pro-interleukin-18 (pro-IL-18) [73,74] into their mature and active forms (IL-1β and IL-18, respectively). The secretion of these cytokines may lead to pyroptosis, a term used to describe the inherently inflammatory process of CASP1-dependent programmed cell death [75,76]. Inflammasome-independent sources of IL-1β have also been suggested to contribute to inflammatory disease pathogenesis; however, very little is known about the molecular regulation of these pathogenic pathways [77].

As previously indicated, several NLRs play a role in the formation of inflammasomes, namely: NLRP1, NLRP3, and NLRC4 [70]. Other less characterized inflammasome structures include NLRP2, NLRP6, NLRP7, NLRP12, as well as AIM2-like receptor (ALR) proteins [78]. Interferon γ-inducible protein 16 (IFL16) has also been suggested to assemble inflammasomes and induce caspase-1 activation in macrophages, indicating differential functions of IFL16, depending on the type of cell infected [79].

NLRP1 was the first NLR family member reported to form an inflammasome complex [80]. NLRP1 has been described to bind directly to its ligand MDP in vitro, with this interaction apparently being sufficient to activate the inflammasome assembly [70]. Genetic variation in the human Nlrp1 gene has been linked to increased susceptibility to certain autoimmune diseases [81], systemic lupus [82] and cancer [179]. Studies have also demonstrated a genetic association of polymorphisms in Nlrp1 gene in driving the tumorigenic process, which leads to an increase in the production of downstream mediators (i.e. CASP1 and IL-1β) in malignant melanoma [83].

NLRP1-like genes are found in most, if not all, mammalian species for which a genome has been sequenced, including primates, rodents, ungulates and marsupials [84]. Humans express only one NLRP1 gene, while the mouse genome contains three Nlrp1 paralogs named Nlrp1a, Nlrp1b and Nlrp1c [79]. Nlrp1a and Nlrp1b contain all domains characteristic of murine NLRs, contrary to the Nlrp1c protein which is truncated so they lack the CARD domains [85]. The murine NLRP1b is involved in the mechanism by which Bacillus anthracis infection activates caspase-1 [86]. NLRP1b also serves as an inflammasome sensor for Toxoplasma gondii, leading to an inflammasome response in rats and, consequently, limiting parasite load and dissemination [87]. Still, more studies are warranted to describe the precise mechanism of T. gondii recognition by NLRP1b.

To date, NLRP3 (also known as cryopyrin and NALP3) is the most fully characterized member of the NLRs family [88]. The NLRP3 inflammasome is activated by a number of factors, which include: Gram-positive bacteria, viruses (such as influenza), fungi and protozoa, toxins (such as hemolysin), ATP, potassium efflux, and reactive oxygen species (ROS) [70,89–91]. In addition to the microbial and endogenous activators mentioned above, RNA and mitochondrial DNA have also been described as NLRP3 activators [92]. NLRP3 lacks a CARD, therefore, cannot recruit procaspase-1 without the presence of the adaptor molecule ASC [73]. NLRP3 interacts with ASC via PYD homophilic interactions [73]. Some studies link various adaptor proteins, such as guanylate-binding protein (GBP) [93,94], thioredoxin (TRX)-interacting protein (TXNIP) [89], amongst others shown to be critical for mammalian host defense. Altogether, the NLRP3 inflammasome integrates multiple signals to protect the host against different forms of cellular stress [95]. Nevertheless, the mechanisms governing the formation and activation of the NLRP3 inflammasomes, in certain cellular contexts, still deserve further investigation.

NLRC4 is also an important sensor for the activation of caspase-1, particularly in macrophages infected with Salmonella strains [96]. This sensor is typically activated by a more streamlined set of ligands, which includes bacterial flagellin and components of the bacterial T3SS (Type 3 secretion system proteins) [97]. NLRC4 appears to detect these ligands by recognizing pathogen derivatives, which are secreted into the host cell cytosol by certain bacterial strains [84].

Impact of NLRs on cancer

Chronic inflammation and cancer onset

Inflammation has a dual role in cancer onset and progression. Pro-inflammatory condition has been described as a crucial state for cancer onset, progression, angiogenesis, and metastasis [98–100], being related to chronic low-grade activation of the immune system as a result of the production of several downstream pro-inflammatory factors [101]. On the other hand, immunosurveillance can prevent cancer onset and limit tumor growth [102,103].

Biomolecules that are produced by tumor-infiltrating immune cells, such as cytokines, proteases, reactive oxygen and nitrogen species, can influence the microenvironment and act as intermediates in these pathological processes [104–106]. The microenvironmental changes caused by the immune infiltrate include alterations (i) in the tumoral
extracellular matrix and (ii) in the interaction between the different cell populations of the tissue, resulting in epigenetic modifications, epithelial–mesenchymal transition (EMT), oncogenes expression promotion and silencing of tumor suppressors [107–110]. Collectively, these alterations may orchestrate cell growth and survival, migration and/or angiogenesis, therefore promoting tumor progression and metastasis [111–113].

One of the most prominent cascades involved in tumor promotion is NF-κB, a key pathway in innate immunity and inflammation, which frequently appears as an interesting therapeutic target [114,115]. Directly linked to NF-κB, inflammasomes and their effector proteins are associated with different chronic pro-inflammatory conditions, and can either promote tumorigenesis or act as key players in immunosurveillance [116,117]. Interestingly, NF-κB also exerts a critical regulatory role during development. Manipulation of NF-κB members in a diverse range of animal models results in severe developmental defects during embryogenesis, very often leading to embryonic lethality [118]. For instance, inactivation of the NF-κB pathway in chicks induces functional alterations of the apical ectodermal ridge, which mediates limb outgrowth [119,120]. In mice, the absence of NF-κB activity leads to prenatal death due to defects in organogenesis and endoderm progression [121,122]. One major protein complex of this pathway, known as IκB kinase (IKK (inhibitor of nuclear factor κB kinase)), directly regulates NF-κB activation also during development of early vertebrates [123]. The IKK complex is mainly composed by two catalytic subunits (IKK1 and IKK2) and one scaffolding molecule (NEMO). IKK2 is the major cytokine-responsive IκB kinase [124,125] and, contrarily, IKK1 seems to be a repressor of NF-κB activity in certain biological and cell-specific conditions [123]. For instance, Ikk1 knockdown in zebrafish embryos leads to head-to-tail malformations due to up-regulation of NF-κB-responsive genes and NF-κB-dependent apoptosis [123]. Conversely, ikk1 overexpression leads to midline structure defects (no tail-like phenotype) associated with the repression of NF-κB activity [126]. Mechanistically, Ikk1 seems to sequester the non-catalytic subunit NEMO from active IKK complexes, therefore blocking NF-κB activation. Indeed, truncation of the NEMO-binding domain (NBD) in Ikk1, as well as increased availability of NEMO in vivo, is able to rescue the ikk1 overexpression phenotype [123]. Altogether, the significance of NF-κB during early development certainly justifies the biological impact of this pathway in the onset and progression of various proliferative diseases, including cancer.

Here, we briefly discuss the inflammation mechanisms driven by distinct NLRs and their association with a substantial number of relevant malignancies. A snapshot of major cancer types associated with each NLR is shown in Figure 2, while a list of reports linking NLRs to a number of cancers is presented in Tables 1 and 2.

**NLRA-associated cancers**

**B-cell lymphoma**

B-cell lymphomas comprise approximately 85% of all non-Hodgkin’s lymphomas (NHL), amongst which the primary mediastinal large B-cell lymphoma (PMBCL), a subtype of diffuse large B-cell lymphoma (DLBCL), sums up approximately 10% of the cases [127]. The incidence of PMBCL is higher in young adults and adolescents, with a metastatic potential to invade surrounding tissues [127]. Analysis of the CIITA sequence in PMBCL patient samples revealed the presence of structural genomic rearrangements, missense, nonsense, and frameshift mutations in 53% of the clinical cases [128]. These alterations led to decreased CIITA protein levels and, consequently, suppression of MHCII on the cell surface [128]. A similar study described that genomic breaks in the CIITA locus were present in 38% of the PMBCL samples and 15% of classical Hodgkin lymphoma (cHL) [129]. These alterations in CIITA sequence are associated with the down-regulation of surface MHC II, and increased expression of ligands of the receptor molecule programmed cell death 1, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) [129]. These data suggest that CIITA has an essential role in PMBCL progression [128,129].

**NLRB-associated cancers**

**Breast cancer**

Breast cancer is the most prevalent cancer in women, accounting for 29% of all diagnosed cancers in females [130]. Little is known about NAIP’s role in breast cancer, but NAIP mRNA levels have been well detected in tumor samples, while no expression is observed in control tissues [131]. In addition, NAIP expression in these malignant tissues is correlated with tumor size, but not with relapse-free survival [131]. More mechanistic studies are still warranted to confirm whether NAIP is relevant to breast cancer biology.

**Colorectal cancer**

Colorectal cancer (CRC) has the third highest cancer incidence worldwide, accounting for 9% of all cases, and is the fourth cause of death by cancer [132,133]. NAIP might also play an important role in preventing CRC onset [134]. Not only NAIP expression in colon cancer samples was found to be lower than in normal mucosa [135] but also,
## Table 1 Summary of reported associations between members of NLRs subfamilies A, B, and C, and cancer progression

| NRL subfamily | Member | Associated cancer | Associated phenotype | Molecular mechanisms | References |
|---------------|--------|-------------------|----------------------|----------------------|------------|
| NLRA          | CIITA  | Primary mediastinal B-cell lymphoma | Tumoral immune evasion | Decrease in surface MHC II and increase in CD274/PDL1 and CD273/PDL2 | [128,129] |
| NLRB          | NAIP   | Breast            | Higher expression in tumor samples | –                     | [131]     |
|               |        | Colorectal        | Lower expression in tumor samples; depleted mice are more susceptible to colitis-associated cancer | Increase in STAT3 expression and failure to activate p53 | [134,135] |
|               |        | Prostate          | Higher expression in advanced prostate cancer submitted to androgen deprivation therapy; possible contribution to docetaxel resistance | Expression is induced by NF-κB | [138]     |
| NLRC          | NOD1   | Breast            | SNPs associates with a higher cancer risk; inhibits ER-dependent tumor growth; deficiency correlates with tumor growth, an increased sensitivity to estrogen-induced cell proliferation, and impaired Nod1-dependent apoptosis; reduced cell proliferation and increased clonogenic potential in vitro | Apoptosis mediated by caspase 8 in a RIP2-dependent mechanism | [142–146] |
|               |        | Colorectal        | Expression in T cells is associated with reduced susceptibility to chemically induced colitis and tumorgenesis; limits inflammation and its induced tumorgenesis | Reduction of inflammation induced tumorgenesis in an IFNγ-mediated mechanism | [150]     |
|               |        | Gastric           | SNPs associated with Helicobacter pylori infection and gastric lesions; up-regulated upon H. pylori infection and associates with a higher inflammatory state in GC | Activation of TRAF3 and suppression of Cdx2 | [160–162] |
| NOD2          | Breast | SNPs associated with a higher cancer risk; reduced cell proliferation and increased clonogenic potential in vitro | – | – | [142,143,146] |
|               |        | Colorectal        | Deficient expression associates with higher susceptibility to experimental models of CRC and induced instability in the composition of gut bacteria; limits inflammation and its induced tumorgenesis | Inhibition of NF-κB and MAPK pathways through the induction of IRF4 | [156,157] |
|               |        | Gastric           | SNPs associated with H. pylori infection and gastric lesions | – | – | [159] |
| NLRC3         | Colorectal | Reduced expression correlated with cancer progression; suppression of cellular proliferation and induction of cell death | Inhibition of the PI3K-mTOR signaling pathway through interaction with PI3K, TRAF6, and mTOR, suppression of c-Myc activity, FoxO3a and FoxO1 | – | – | [148,151] |
| NLRC4         | Breast | Poor prognosis | Upon obesity, expression in myeloid cells leads to IL-1β expression and VEGFA-dependent angiogenesis | – | – | [141] |
|               | Colorectal | Reduced expression correlates with cancer progression; mediates higher proliferation and apoptosis during tumorgenesis in casp-1 deficient mice | – | – | [148] |
| NLRC5         | Colorectal | Reduced expression correlates to impaired CD8⁺ T-cell activation and poor patient prognosis; higher cancer risk | Impaired MHC I pathway | – | – | [149,153–155] |
|               | Gastric | Expression associated with lymph nodes and tumor node metastasis | – | – | [162] |

Abbreviations: Cdx2, caudal-related homeobox 2; CRC, colorectal cancer; ER, estrogen receptor; GC, gastric cancer; PDL1, programmed death ligand 1; PDL2, programmed death ligand 2; VEGFA, vascular endothelial growth factor A.

Based on a model of colitis-associated cancer, mice lacking NAIP paralogs (Naip1-6) display a higher susceptibility for CRC in an inflammation-independent mechanism [134]. Furthermore, these knockout mice displayed increased STAT3 expression and failed to activate p53 upon carcinogen exposure [134]. This suggests that NAIPs may act as tumor suppressors in vivo by inducing apoptosis in carcinogen-affected cells.
Table 2 Summary of reported associations between NLRP and atypical genes and cancer progression

| NRLP subfamily | Member | Associated cancer | Associated phenotype | Molecular mechanisms | References |
|----------------|--------|-------------------|----------------------|---------------------|------------|
| NLRP1          | Skin   | Promotes migration, IL-1β processing, evasion of apoptosis and hyperplasia | IL-1β processing, Caspase-1 cleavage, inhibition of caspase-2, -3/7, and -9 activities | [209,210-212,214] |
| Prostate       | SLK    | Up-regulated in experimental model of inflammation by formalin injection in situ | Increase in IL-1β, IL-18, and caspase-1 expressions | [205] |
| Cervix         | SNP    | SNPs associated with lower oncogenesis related to HPV infection | – | [166] |
| NLRP3          | Cervix | SNPs associated with lower oncogenesis related to HPV infection, highly expressed in an inflammatory context upon LPS treatment | Caspase-1 cleavage, IL-1β expression and processing | [166,167] |
| Colorectal     | Expression in macrophages: promotes invasion, migration, metastasis of tumor cells | Expression in macrophages: leads to caspase-1 cleavage, NLRP3–ASC–caspase-1 complex formation, and IL-1β processing and secretion | [169,171,173–175] |
| Gastric        | SNPs associated with higher cancer risk; expression in macrophages was found to be associated with aggressiveness | IL-1β secretion | [190] |
| Colorectal     | Promotes EMT, higher migratory and invasive potential, proinflammatory signaling, IL-1 β production, ionizing radiation (IR) treatment resistance, cellular senescence after IR, resistance to apoptosis | IL-1β processing, AKT/PTEN pathway and Stat3 activation | [197–200] |
| NLRP6          | Skin   | Promotes migration, IL-1β processing and hyperplasia | IL-1β processing, Caspase-1 cleavage, NFκB pathway | [211,212,214] |
| NLRP7          | Endometrial | Correlates with depth of tumor invasion | – | [187] |
| Gastric        | Deficiency associated with lymph node metastasis and poor overall survival | Senescence mediated by P21 and Cyclin D1 | [191] |
| NLRP12         | Colorectal | Its depletion leads to higher tumor burden | Modulation of noncanonical NF-κB through TRAF3 and NIF, AKT and ERK pathways | [181,182] |
| Atypical       | NWD1   | Prostate | Expression correlates with tumor progression | Its expression is modulated by SRY, regulates PDEF expression, its depletion reduces AR levels and androgen-responsive genes | [219] |

Abbreviations: AR, androgen receptor; HPV, human papillomavirus; IL-22BP, IL-22 binding protein; LPS, lipopolysaccharide; NK cell, natural killer cell; PDEF, prostate-derived Ets factor; SRY, sex-determining region Y.

Prostate cancer
Prostate cancer (PCa) is the most common cancer in men [136,137]. Advanced PCa, submitted to androgen deprivation therapy, displays increased NAIP expression, which may possibly contribute to docetaxel resistance [138]. One possible explanation is that androgens generally inhibit responsive elements in NF-κB transcription factors promoters, decreasing their expression [138,139]. Therefore, it was verified by chromatin immunoprecipitation (ChIP) that, upon hormonal deprivation, NF-κB largely interacts with κB-like sites along the NAIP locus to promote its transcription activation [138]. These data suggest that NAIP levels may correlate with drug resistance in the treatment of PCa, but further experiments are needed to explore the role of NAIP in these mechanisms.

NLRC-associated cancers
Breast cancer
Obesity has been associated with a poor prognosis of breast cancer patients, since adipose cells stimulate angiogenesis and synthesize estrogen, a primary female hormone that impacts tumor growth and metastatic potential [140]. For instance, in an orthotopic model, obese mice displayed higher tumor-infiltrating myeloid cells content and higher
tumor-angiogenesis [141]. Interestingly, myeloid cells from obese mice display increased NLRC4 expression and, consequently, IL-1β production. Cross-talk between tumor tissue and immune infiltrates also leads to vascular endothelial growth factor A (VEGFA)-mediated angiogenesis in an NLRC4-dependent manner, therefore driving disease progression [141].

A number of NOD1 and NOD2 SNPs have been associated with a higher risk of cancer development in many malignancies [142,143]. Although no tumor suppressor activity has been described for NOD2, NOD1 seems to have important tumor suppressor activity in estrogen receptor (ER)-dependent breast cancer, using an SCID mouse xenograft model [144]. In ER-positive MCF-7 cells, NOD1 deficiency correlates with tumor growth, an increased sensitivity to estrogen-induced cell proliferation and impaired Nod1-dependent apoptosis. Correspondingly, in the same cells, NOD1 overexpression inhibited ER-dependent tumor growth and reduced estrogen proliferative response in vitro [144]. Apparently, Nod1-dependent apoptosis is mediated by a caspase 8-cascade in an RIP2-dependent manner [145]. More recently, it has been described that overexpression of either NOD1 or NOD2, in the triple negative Hs578T cells, is able to reduce cell proliferation but increase clonogenic potential in vitro [146]. The proteomic profile of these overexpressing cells suggests the involvement of several inflammation- and stress-related pathways (intersecting NF-κB, PI3K and MAPK cascades) in the modulation of protein degradation processes, cell cycle and cellular adhesion [147]. The disruption of these critical systems suggests a functional link between NOD1/NOD2 and the proliferation and migration of triple negative breast cancer cells [147]. Although NOD1 tumor suppressive role is evidenced in ER-dependent tumors [144], both NOD1 and NOD2 appear to be relevant for the aggressive potential of breast cancer in vitro.

CRC

The expression of certain NLRCs has also been found to be modulated in CRC [148–150]. A combined analysis of TCGA (http://cancergenome.nih.gov) and Oncomine (https://www.oncomine.org) datasets, with mRNA expression analysis of tissue samples, revealed that NOD1 and NOD2 expression is usually increased, while NLRC3 and NLRC4 expression is reduced in CRC [148]. Furthermore, TCGA data analysis revealed that NLRC3 expression inversely correlates with the American Joint Committee CRC staging [148]. Based on this staging, CRC is classified from stage I to IV in which (i) stage I tumors have breached beyond the inner lining of the colon, (ii) stage II tumors invaded the muscular wall of the colon, (iii) stage III tumors have reached the lymph nodes and (iv) stage IV tumors have metastasized to other organs besides the lymph nodes [148]. This correlation might be explained by recent reports describing the link between NLRC3 and the concomitant suppression of cellular proliferation and induction of cell death through the inhibition of the PI3K-mTOR signaling pathway in different node points [151]. Interestingly, NLRC3 knockout mice, treated with azoxymethane and dextran sodium sulfate (colitis-associated CRC model), display an increased C-MYC expression and FoxO3a and FoxO1 phosphorylation (effectors of the PI3K-AKT pathways) [151]. Likewise, caspase-1-deficient mice submitted to the same treatments show increased epithelial cell proliferation in early stages of oncogenesis, and apoptosis evasion in additional stages in an NLRC4-dependent manner [152].

NLRC deficiencies are also correlated to immunosurveillance escape-mediated tumor progression [149]. Gene mutations, polymorphisms, loss of copy numbers, and methylation of the MHC class I transactivator NLRC5 have been associated with MHC I pathway disruption and a higher cancer risk [149]. It is interesting to note a correlation between reduced NLRC5 expression and higher CRC risk, especially in mismatch repair-deficient tumors [153–155]. Moreover, it has been proposed that reduced NLRC5 expression also correlates to impaired CD8+ T-cell activation and poor patient prognosis [149].

Furthermore, NOD1 expression in T cells has been associated with a reduced susceptibility to chemically induced colitis and subsequent tumorigenesis, by limiting inflammation-induced tumorigenesis in an IFNy-dependent mechanism [150]. Similarly, NOD2 deficient mice appear to be more susceptible to experimental models of CRC [156]. Both NOD1 and NOD2 can inhibit NF-κB and MAPK pathways through induction of IFR4 [156] and, apparently, have a role in the suppression of inflammation-induced tumorigenesis [156]. Furthermore, NOD2 deficient mice are seemingly more prone to colitis and colitis-related cancer due to induced instability in the composition of gut microbiome [157]. This increased susceptibility to inflammation could be prevented by (i) microbiota transplantation, (ii) antibiotics or (iii) anti-IL-6 neutralizing antibody treatment [157]. These findings reiterate the notion that NLRCs also influence tissue microenvironment and suppress CRC tumorigenesis.

Gastric cancer

Helicobacter pylori infection is a strong risk factor for gastric cancer (GC) [158]. NOD1- and NOD2-specific SNPs have been associated with H. pylori infection and gastric lesions [159]. In this context, expression of the epithelial-specific transcription factor CDX2 is known to contribute to intestinal metaplasia (an event that precedes...
GC) and to be induced by H. pylori infection [160]. The NF-κB pathway has been implicated in induction of CDX2 expression [160]. In contrast, NOD1-dependent activation of TRAF3, a negative regulator of NF-κB, may suppress CDX2 expression [160]. This is somewhat contradictory to the findings in which, upon H. pylori infection, NOD1 is up-regulated and associated with a higher inflammatory state in GC [161].

NLRC5 expression has been correlated with lymph nodes and tumor node metastasis in GC [162]. As a result, NLRC5 has been considered as an independent risk factor for the prognosis of GC patients [162]. The orchestrated expression of NLRC5, as well as of other NLRC proteins, may play an important role in GC onset, but more detailed studies are needed to better dissect their actual contribution to GC.

**NLRP-associated cancers**

Amongst the NLRP subfamily members, the role of NLRP3 in cancer is the most well characterized (extensively revised in [163]). Here, we describe some of the main findings linking NLRPs to different human malignancies.

**Cervical cancer**

Cervical cancer is the second most common cancer type in women [164]. It has been found that persistent Human Papillomavirus (HPV) infection, associated with chronic inflammation, may lead to cancer onset [165]. Particularly, polymorphisms in NLRP1, NLRP3 and IL-18 have been associated with a lower HPV persistence and associated oncogenesis [166]. Using an inflammation model, human cervical cancer cells, positive for HPV-16 and treated with lipopolysaccharide (LPS), have indeed displayed increased levels of NLRP3, IL-1β, processed IL-1β, and cleaved caspase-1 [167].

**CRC**

Inflammation is highly associated with the onset of CRC. Inflammatory bowel disease (IBD), which comprises diseases such as ulcerative colitis and Crohn’s disease, is mainly a chronic inflammatory condition which is known to increase the overall risk of developing CRC by 4- to 20-fold [132]. NLRP3 has been proposed to be a link between IBD and CRC (reviewed in [168]). Interestingly, high-fat diet has also been associated with NLRP3 activation and increased tumor susceptibility [162,169]. High-fat diet leads to an increase in deoxycholic acid levels in the intestine, which, in turn, disrupts the cell monolayer integrity by decreasing the expression of the tight junction protein ZO-1 [170]. This disruption in the mucosal barrier leads to an increased tissue inflammation, mediated by NLRP3, and further polarization of M2 macrophages [162]. Likewise, azoxymethane-treated mice submitted to a cholesterol-rich diet show increased tissue inflammation and higher susceptibility to tumor development [169]. In fact, cholesterol inhibits the activity of AMPKα in macrophages, resulting in increased levels of mitochondrial ROS [169]. An oxidative microenvironment may then activate NLRP3, leading to (i) inflammasome formation, (ii) caspase-1 cleavage and (iii) IL-1β processing and secretion [169]. This cascade of events can be partially reverted by NLRP3 depletion [169].

NLRP3 expression has also been found in macrophages infiltrated in CRC tissues, and the inhibition of NLRP3 pathway leads to decreased tumor cell migration, invasion and metastatic potential [171]. These data are supported by the evidence that treatment with a small-molecule AMPK activator (GL-V9), which acts as an anti-inflammatory molecule on macrophages, triggers autophagy and NLRP3 degradation, providing a protective effect against colitis and CRC [172].

Although NLRP3 expression in tissue-infiltrated macrophages has been associated with higher susceptibility to CRC and its aggressiveness, its role in tumor cells is, at a first glance, controversial. NLRP3 has been found, for instance, to be highly expressed in the SW620 mesenchymal-like CRC cell line [173]. Moreover, HCT116 and HT29 epithelial-like CRC cell lines, when submitted to EMT through the treatment with TNF-α and TGF-β1, displayed an increase in NLRP3 expression mediated by NF-κB [173]. In contrast, NLRP3 or CASP1 deficient mice are more susceptible to the CRC burden induced by azoxymethane-DSS-induced inflammation model [174]. This phenotype is associated with lower IL-18 expression levels and, consequently, impairment of IFN-γ expression and suppression of STAT1 activation [174]. In addition, NLRP3 knockout mice display augmented liver metastasis [175], which is also due to the impairment of IL-18 signaling. This suppression affects Fas ligand (FasL) expression in natural killer cells (NK cells), thus compromising their ability to kill FasL-sensitive tumor cells [175].

In accordance with the current data, NLRP3 expression might be explored for the prevention of CRC. One example is its role as an effector of TRAIL (tumor necrosis factor related apoptosis-inducing ligand), an apoptosis-inducing protein whose use for cancer treatment has been currently evaluated [176–178]. In this context, mice submitted to the azoxymethane-DSS CRC model and treated with recombinant TRAIL displayed inhibition of macrophage recruitment to the damaged mucosa, therefore diminishing acute inflammation [176]. At the same time, TRAIL promoted tissue regeneration by NLRP3 activation, which induced IL-18 expression and promoted IL-1β secretion and
Glioblastoma multiforme (GBM), also known as Grade IV astrocytoma, is the most common type of brain tumors in adults, comprising approximately 17% of the cases [192,193]. GBMs are extremely aggressive tumors, displaying metastasis and poor overall survival [191]. The incidence rates of endometrial cancer have increased during last few decades and, nowadays, is considered the sixth most common cancer in women [183]. Its occurrence is associated with precursor hyperplasic lesions in more than 40% of cases [184]. Although IL-1 has been described to have an important role in endometriosis (a chronic inflammatory condition in which endometrial tissue grows outside the uterine cavity) [185,186], little is known about the inflammasome’s role in the development of this endometrial condition. The only available data so far refer to a statistical correlation observed between NLRP7 and the depth of the tumor invasion in the surrounding normal tissue [187], which is indeed promising but requires more detailed investigations.

NLRP3 is the fourth most common type of cancer, and it is responsible for the second highest rate of cancer-related deaths [188]. Specific SNPs in some NLRP subfamily members, such as NLRP3 and NLRP12, have been associated with increased risk of H. pylori infection (one of GCs most prominent risk factors) and also to GC itself [189]. H. pylori-challenged cells can lead to simultaneous down-regulation of NLRP9 and NLRP12 and up-regulation of the canonical NF-κB pathway [189]. Indeed, NLRP12 is a known inhibitor of the NF-κB pathway, and its inhibition might contribute to the maintenance of an active state of this signaling cascade [189].

NLRP3 expression in macrophages has been found to be associated with GC aggressiveness [190]. In a physiological scenario, the microRNA miR-22 (expressed in the gastric mucosa) inhibits NLRP3 expression and suppresses inflammation [190]. H. pylori infection suppresses miR-22, increasing NLRP3 expression which, in turn, leads to IL-1β secretion and promotes the proliferation of epithelial cells and GC tumorigenesis [190]. Contrarily, it has been reported that NLRP6 expression is reduced in ~75% of the primary GC cases, and is associated with lymph node metastasis and poor overall survival [191]. NLRP6 expression may suppress cancer cell proliferation by inducing senescence in a mechanism mediated by p21 and cyclin D1. In fact, overexpression of NLRP6, along with the inactivation of NF-κB and Mdm2, activates the p14ARF-p53 pathway and promotes senescence of GC cells [191]. This particular mechanism may be potentially explored for the GC treatment.

Glioblastoma multiforme

Glioblastoma multiforme (GBM), also known as Grade IV astrocytoma, is the most common type of brain tumors in adults, comprising approximately 17% of the cases [192,193]. GBMs are extremely aggressive tumors, displaying highly infiltrative growth patterns and a very poor prognosis, with a median overall survival of 15–18 months after diagnosis [192,194,195].

The tumor microenvironment plays a crucial role in GBM progression. In particular, the presence of activated microglial and macrophage cells are associated with higher aggressive phenotypes (reviewed in [196]). Amongst the soluble factors secreted by microglial cells, IL-1 is known to activate GBM cells, partially due to the activation of TGFβ pathway, and also to alter their secretome, resulting in the up-regulation of interleukin-8 (IL-8) and C–C motif chemokine ligand 2 (CCL2), and the down-regulation of collagen type IV α2 chain (COL4A2) [197]. In human GBM cell lines, NLRP3 is also responsible by IL-1β processing [198]. IL-1 production in these cells leads to activation of the transcriptional factor Stat3, resulting in increased cellular migration and establishing a mesenchymal phenotype [198].

NLRP3 has been positively correlated to higher histological grades in astrocytomas [199]. NLRP3 overexpression in human GBM cells promotes invasion, migration, proliferation, resistance to apoptosis and EMT via activation of canonical NF-κB pathway, and also to alter their secretome, resulting in the up-regulation of interleukin-8 (IL-8) and C–C motif chemokine ligand 2 (CCL2), and the down-regulation of collagen type IV α2 chain (COL4A2) [197]. In human GBM cell lines, NLRP3 is also responsible by IL-1β processing [198]. IL-1 production in these cells leads to activation of the transcriptional factor Stat3, resulting in increased cellular migration and establishing a mesenchymal phenotype [198].

NLRP3 has been positively correlated to higher histological grades in astrocytomas [199]. NLRP3 overexpression in human GBM cells promotes invasion, migration, proliferation, resistance to apoptosis and EMT via activation
of the AKT pathway [199]. In addition, NLRP3 expression has been linked to resistance against ionizing radiation therapy, leading to an increased number of senescent cells after this treatment [200]. Interestingly, this phenotype is partially reversed by NLRP3 inhibition [200]. Therefore, NLRP3 looks like a promising therapeutic target, and the use of NLRP3 inhibitors, such as β-Hydroxybutyrate or certain miRNAs, have been considered for GBM treatment [201,202].

PCa
Studies have shown that the presence of infiltrating immune cells in prostatic tissues is inversely correlated to PCa progression [203,204]. Prostatic inflammation, experimentally induced by intra-prostatic injection of formalin, leads to increased NLRP1 expression and consequent increase in IL-1β, IL-18 and caspase-1 levels [205]. Highly metastatic PCa cells (DU145 and PC-3) secrete IL-18 binding protein (IL-18BP) after IFN-γ stimulation [206]. Coincidentally, IL-18BP levels in patient sera have been correlated with PCa aggressiveness [206]. This suggests that IL-18 neutralization might be a mechanism by which PCa cells bypass immunesurveillance and promote tumor development.

Skin cancer
Approximately 2–3 million skin cancers cases are diagnosed each year and their incidence has increased over the last decades [207]. Skin tumors can be classified as non-melanomas (derived from keratinized epithelial cells) or melanomas (derived from melanocytes) [190,191]. Melanoma accounts for 2% of the cases, being the most aggressive type of skin cancer, accounting for almost 10,000 deaths per year [207,208].

Although inflammation may contribute to defense mechanisms against tumor onset, chronic skin inflammation can promote the development of benign and malignant lesions. For instance, using organotypic ex vivo skin models, treatment with IL-1 leads to an increase in epidermal thickness due to the proliferation of keratin-10- and involucrin-positive keratinocytes in the basal layer [209]. This higher proliferation rate is accompanied by an increased expression of the stress markers, S100 calcium binding proteins A8/9 (S100A8/9) and S100 calcium binding protein A7 (S100A7), known to be highly expressed in skin cancers, suggesting that inflammasome-dependent IL-1 production may be sufficient to induce skin hyperplasia [209].

The skin typically displays high expression levels of NLRP1, and gain-of-function mutations along this gene can lead to skin hyperplasia, including multiple self-healing palmoplantar carcinoma (MSPC) and familial keratosis lichenoides chronic (FKLC) [209]. NLRP1 knockdown in metastatic melanoma cell lines induces lower caspase-1 activity and IL-1β production/secretion, but it also results in increased caspase-2, -3/7 and -9 activities, therefore promoting apoptosis [210]. Likewise, activation of NLRP1, but not of NLRP3, decreases caspase-2, -3/7, and -9 activities and consequent evasion from apoptosis [210].

Ultraviolet B (UVB) radiation is considered a major risk factor for skin cancer. Both NLRP1 and NLRP3 have been implicated in the first response to UVB in human keratinocytes [211,212]. UVB induces NLRP1 and NLRP3 expression, leading to inflammation onset through extensive IL-1β secretion [211,212]. Furthermore, specific SNPs in both NLRP1 and NLRP3 have been associated with susceptibility to nodular melanoma [213]. More recently, CRISPR inactivation of both NLRP genes revealed that NLRP1 is, in fact, the main responsible for the cellular pro-inflammatory response against UVB radiation [214]. Nevertheless, a compound isolated from Nigella sativa seeds, called thymoquinone (2-isopropyl-5-methyl benzo-1,4-quione), was found to inhibit migration of melanoma cells through inhibition of NLRP3 expression and its related cascade, leading to a decrease in caspase-1 cleavage as well as IL-1 and IL-18 levels [215]. This suggests that both NLRP proteins may be relevant for the onset and progression of skin cancer.

NLR-related proteins and cancer
PCa
Other cytosolic receptors, which are not fully categorized as NLRs but still share structural similarities, may also be of clinical relevance in the context of cancer development. For instance, NWD1 (NACHT and WD repeat domain-containing protein 1) is an NLR-related protein which carries a conserved NACHT domain and WD40 repeats instead of LRRs at the C-terminus [216]. Sequence homology analysis suggests this protein may be a novel NLR family member [216]. NWD1 also share homology with Apaf1 (Apoptotic peptidase activating factor 1), a cytoplasmic receptor that also possesses WD40 repeats instead of LRRs, and it is involved in caspase 9-mediated apoptosis [217,218]. It has been reported that NWD1 expression elevates in the course of PCa progression. In vitro experiments demonstrated that sex-determining region Y (SRY) proteins may regulate the NWD1 expression, which in turn regulates PDEF (prostate-derived Ets factor), a transcription factor which is known to bind and modulate the androgen receptor (AR). Furthermore, NWD1 depletion reduces AR levels and androgen-responsive genes, suggesting a role for NWD1 in PCa via AR deregulation [219].
Conclusion

Based on the data here described, we summarized how deregulation in the balance of NLR-related signals may lead to the onset of several types of cancer. Despite all the knowledge accumulated regarding these cytosolic receptors, the functional domains, ligand specificity and signal transduction events directed by each particular family member still remain to be better elucidated. At the same time, new atypical NLR members may continue to be uncovered, adding another layer of complexity to the studies involving innate immune sensors. A more in-depth understanding of how these receptors signal through different pathways, and how they interact to achieve a global impact in diverse pathologies, such as cancer, will be seminal to develop better diagnostic and prognostic tools, as well as more effective therapeutic strategies.

Funding

This work was supported by CAPES (Federal Agency for Superior Education and Training) research funding agency [grant number 88887.091759/2015-00 (to F.J.V.); FAPESP (São Paulo State Foundation for Research) [grant number 2016/05311-2 (to M.C.S.); CNPq (National Research Council) [grant number 148684/2013-0; 457201/2013-2 (to M.C.S.); BNDES (Brazilian National Bank for Economic and Social Development) [grant number 09.2.1066.1 (to M.C.S.); FINEP (Project Financing Agency) [grant number 01.06.0664.00; 01.08.0622.00 (to M.C.S.); MCTI (Science, Technology and Innovation Ministry) (to M.C.S.); MS-DECIT (Science and Technology Department of the Health Ministry) (to M.C.S.); and a Special Visiting Researcher (PVE) grant from the ‘Science without Borders’ Program (CAPES, Brazil) [grant number 88887.091759/2015-00 (to R.G.C.)).

Competing interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

AD, acidic transactivation domain; AR, androgen receptor; ASC, apoptosis-associated speck-like protein containing CARD; AT, acetyltransferase; CARD, caspase recruitment domain; CASP1, caspase 1; CIITA, class II major histocompatibility complex transactivator; CRC, colorectal cancer; DAMP, danger-associated molecular pattern; EMT, epithelial–mesenchymal transition; ER, estrogen receptor; FastL, Fas ligand; GBM, glioblastoma multiforme; GC, gastric cancer; HPV, human papillomavirus; IKK, inhibitor of nuclear factor κB kinase; IRF, interferon response factor; IκB, inhibitor of nuclear factor κB; LRR, leucine-rich repeat; MAPK, mitogen-activated protein kinase; MDP, muramyl dipeptide; NAIP, NLR family apoptosis inhibitory protein; NACH, NAIP (neuronal apoptosis inhibitory protein), C2TA (MHCI class 2 transcription activator), HET-E (incompatibility locus protein from Podospora anserina) and TP1 (telomerase-associated protein); NEMO, NF-κB essential modulator; NF-κB, nuclear factor κB; NLR, NACHT and LRR domain containing protein; NOD1, nucleotide oligomerization domain 1; NOD2, nucleotide oligomerization domain 2; NWD1, NACHT and WD repeat domain-containing protein 1; PAMP, pathogen-associated molecular pattern; PCa, prostate cancer; PGN, peptidoglycan; PMBCL, primary mediastinal large B-cell lymphoma; PRR, pattern recognition receptor; PYD, pyrin domain; RIP2, receptor-interacting protein 2; ROS, reactive oxygen species; TAK1, TGF-β-activated kinase 1; TLR, Toll-like receptor; TRAIL, tumor necrosis factor related apoptosis-inducing ligand; UVB, ultraviolet B.

References

1 Zhong, Y., Kinio, A. and Saleh, M. (2013) Functions of NOD-like receptors in human diseases. Front. Immunol. 4, 333, https://doi.org/10.3389/fimmu.2013.00333
2 Akira, S., Uematsu, S. and Takeuchi, O. (2006) Pathogen recognition and innate immunity. Cell 124, 783–801, https://doi.org/10.1016/j.cell.2006.02.015
3 Muñoz-Wolf, N. and Lavelle, E.C. (2016) Innate immune receptors. Methods Mol. Biol. 1417, 1–43, https://doi.org/10.1007/978-1-4939-3566-6_1
4 Kanneganti, T.-D., Lamkanfi, M. and Núñez, G. (2008) The NLR gene family: a standard nomenclature. Immunity 27, 549–559, https://doi.org/10.1016/j.immuni.2007.10.002
5 Ting, J.P.-Y., Lownering, R.C., Alnemri, E.S., Berlin, J., Boss, J.M., Davis, B.K. et al. (2008) The NLR gene family: a standard nomenclature. Immunity 28, 285–287, https://doi.org/10.1016/j.immuni.2008.02.005
6 Sirisinha, S. (2011) Insight into the mechanisms regulating immune homeostasis in health and disease. Asian Pac. J. Allergy Immunol. 29, 1–14
7 Creagh, E.M. and O’Neill, L.A.J. (2006) TLRs, NLRs and RLRs: a Trinity of pathogen sensors that co-operate in innate immunity. Trends Immunol. 27, 352–357, https://doi.org/10.1016/j.it.2006.06.003
8 Kim, Y.K., Shin, J.S. and Nahm, M.H. (2016) NOD-like receptors in infection, immunity, and diseases. Yonsei Med. J. 57, 5–14, https://doi.org/10.3349/ymj.2016.57.1.5
9 Hoque, R. and Mehal, W.Z. (2015) Inflammasomes in pancreatic physiology and disease. Am. J. Physiol. Gastrointest. Liver Physiol. 308 (8), G643–G651, https://doi.org/10.1152/ajpgi.00388.2014
10 Kufer, T.A., Banks, D.J. and Philpott, D.J. (2006) Innate immune sensing of microbes by nod proteins. Ann. N.Y. Acad. Sci. 1072, 19–27, https://doi.org/10.1196/annals.1326.020

© 2019 The Author(s). This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution License 4.0 (CC BY).
39 Stutz, A., Golenbock, D.T. and Latz, E. (2009) Science in medicine Inflammomasomes: too big to miss. *J. Clin. Invest.* **119**, 3502–3511, https://doi.org/10.1172/JCI40599
40 Tian, X., Pascal, G. and Monget, P. (2009) Evolution and functional divergence of NLRP genes in mammalian reproductive systems. *BMC Evol. Biol.* **9**, 202, https://doi.org/10.1186/1471-2148-9-202
41 Kufer, T.A., Kremer, E., Adam, A.C., Philpott, D.J. and Sansonetti, P.J. (2008) The pattern-recognition molecule Nod1 is localized at the plasma membrane at sites of bacterial interaction. *Cell. Microbiol.* **10**, 477–486
42 Legrand-Poels, S., Kustermans, G., Bex, F., Kremer, E., Kufer, T.A. and Piette, J. (2007) Modulation of Nod2-dependent NF-kappaB signaling by the actin cytoskeleton. *J. Cell Sci.* **120**, 1299–1310, https://doi.org/10.1242/jcs.03424
43 Lee, J., Tatoli, I., Wojtal, K.A., Vavricka, S.R., Philpott, D.J. and Girardin, S.E. (2009) pH-dependent internalization of muramyl peptides from early endosomes enables Nod1 and Nod2 signaling. *J. Biol. Chem.* **284**, 23818–23829, https://doi.org/10.1074/jbc.M109.033670
44 Marina-García, N., Franchi, L., Kim, Y.-G., Hu, Y., Smith, D.E., Boons, G.-J. et al. (2009) Clathrin- and dynamin-dependent endocytic pathway regulates muramyl dipeptide internalization and NOD2 activation. *J. Immunol.* **182**, 4321–4327, https://doi.org/10.4049/jimmunol.0801217
45 Paik, D., Monahan, A., Caffrey, D.R., Elling, R., Goldman, W.E. and Silverman, N. (2017) SLC46 family transporters facilitate cytosolic innate immune recognition of monomeric peptidoglycans. *J. Immunol.* **199**, 263–270, https://doi.org/10.4049/jimmunol.1600409
46 Irving, A.T., Mihuro, H., Kufer, T.A., Lo, C., Wheeler, R., Turner, L.J. et al. (2014) The immune receptor NOD1 and kinase RIP2 interact with bacterial peptidoglycan on early endosomes to promote autophagy and inflammatory signaling. *Cell Host Microbe* **15**, 623–635, https://doi.org/10.1016/j.chom.2014.04.001
47 Nakamura, N., Lii, J.R., Phung, Q., Jiang, Z., Bakalarcsik, C., de Mazière, A. et al. (2014) Endosomes are specialized platforms for bacterial sensing and NOD2 signalling. *Nature 509*, 240–244, https://doi.org/10.1038/nature13133
48 Sasawatari, S., Okamura, T., Kasumi, E., Tanaka-Furuyama, K., Yanobu-Takanashi, R., Shirasawa, S. et al. (2011) The solute carrier family 15A4 regulates TLR9 and NOD1 functions in the innate immune system and promotes colitis in mice. *Gastroenterology* **140**, 1513–1525, https://doi.org/10.1053/j.gastro.2011.01.041
49 Caruso, R., Warner, N., Inohara, N. and Núñez, G. (2014) NOD1 and NOD2: signaling, host defense, and inflammatory disease. *Immunity 41*, 898–908, https://doi.org/10.1016/j.immuni.2014.12.010
50 Kobayashi, K., Inohara, N., Hernandez, L.D., Galán, J.E., Núñez, G., Janeway, C.A. et al. (2002) RICK/Rip2/CARDIAK mediates signalling for receptors of the innate and adaptive immune systems. *Nature 416*, 194–199, https://doi.org/10.1038/416194a
51 McCarthy, J.V, Ni, J. and Dixit, V.M. (1998) RIP2 is a novel NF-kappaB-activating and cell death-inducing kinase. *J. Biol. Chem.* **273**, 16968–16975, https://doi.org/10.1074/jbc.273.27.16968
52 Marinis, J.M., Homer, C.R., McDonald, C. and Abbott, D.W. (2011) A novel motif in the Crohn’s disease susceptibility protein, NOD2, allows TRAF4 to down-regulate innate immune responses. *J. Biol. Chem. 286*, 1938–1950, https://doi.org/10.1074/jbc.M110.189308
53 Kim, J.-Y., Omori, E., Matsumoto, K., Núñez, G. and Ninomiya-Tsuji, J. (2008) TAK1 is a central mediator of NOD2 signaling in epidermal cells. *J. Biol. Chem.* **283**, 137–144, https://doi.org/10.1074/jbc.M704746200
54 Hasegawa, M., Fujimoto, Y., Lucas, P.C., Nakano, H., Fukase, K., Núñez, G. et al. (2008) A critical role of RICK/RIP2 polyubiquitination in Nod-induced NF-kappaB activation. *EMBO J.* **27**, 373–383, https://doi.org/10.1038/sj.emboj.7601962
55 Hsu, Y.-M.S., Zhang, Y., You, Y., Wang, D., Li, H., Duramad, O. et al. (2007) The adaptor protein CARD9 is required for innate immune responses to intracellular pathogens. *Nat. Immunol.* **8**, 198–205, https://doi.org/10.1038/nri1426
56 Kobayashi, K.S., Chamailard, M., Ogura, Y., Henegarí, G., Inohara, N., Núñez, G. et al. (2005) Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. *Science 307*, 731–734, https://doi.org/10.1126/science.1104911
57 Travassos, L.H., Carneiro, L.A.M., Ramjeet, M., Hussey, S., Kim, Y.-G., Magalhães, J.G. et al. (2010) Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry. *Nat. Immunol.* **11**, 55–62, https://doi.org/10.1038/ni.1823
58 Cooney, R., Baker, J., Brain, O., Danis, B., Pichulik, T., Allan, P. et al. (2010) NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. *Nat. Med.* **16**, 90–97, https://doi.org/10.1038/nm.2069
59 Homer, C.R., Kab, A., Marina-García, N., Sreevatsi, A., Nesivicek, A.I., Nickerson, K.P. et al. (2012) A dual role for receptor-interacting protein kinase 2 (RIP2) kinase activity in nucleotide-binding oligomerization domain 2 (NOD2)-dependent autophagy. *J. Biol. Chem.* **287**, 25565–25576, https://doi.org/10.1074/jbc.M111.328635
60 Keestra-Gounder, A.M. and Tsoilis, R.M. (2017) NOD1 and NOD2: beyond peptidoglycan sensing. *Trends Immunol.* **38**, 758–767, https://doi.org/10.1016/j.it.2017.07.004
61 Keestra-Gounder, A.M., Byndloss, M.X., Seyffert, N., Young, B.M., Chávez-Arroyo, A., Tsai, A.Y. et al. (2016) NOD1 and NOD2 signalling links ER stress with inflammation. *Nature 532*, 394–397, https://doi.org/10.1038/nature17631
62 Bernales, S., McDonald, K.L. and Walter, P. (2006) Autophagy counterbalances endoplasmic reticulum expansion during the unfolded protein response. *PLoS Biol.* **4**, e423, https://doi.org/10.1371/journal.pbio.0040043
63 Ding, W.-X., Ni, H.-M., Gao, W., Hou, Y.-F., Melan, M.A., Chen, X. et al. (2007) Differential effects of endoplasmic reticulum stress-induced autophagy on cell survival. *J. Biol. Chem.* **282**, 4702–4710, https://doi.org/10.1074/jbc.M609267200
64 Ogata, M., Hino, S., Saito, A., Morikawa, K., Kondo, S., Kanemoto, S. et al. (2006) Autophagy is activated for cell survival after endoplasmic reticulum stress. *Mol. Cell. Biol.* **26**, 9220–9231, https://doi.org/10.1128/MCB.01453-06
65 Lee, W.-S., Yoo, W.-H. and Chae, H.-J. (2015) ER stress and autophagy. *Curr. Mol. Med.* **15**, 735–745, https://doi.org/10.1016/j.cjm.2017.11.036
66 Lilienbaum, A. (2013) Relationship between the proteasomal system and autophagy. *Int. J. Biochem. Mol. Biol.* **4**, 1–26
67 Pashenkov, M.V, Dagil, YA. and Pneinig, B.V. (2018) NOD1 and NOD2: Molecular targets in prevention and treatment of infectious diseases. *Int. Immunopharmacol.* **54**, 385–400, https://doi.org/10.1016/j.intimp.2017.11.036
Afonina, I.S., Zhong, Z., Karin, M. and Beyaert, R. (2017) Limiting inflammation—the negative regulation of NF-κB and the NLRP3 inflammasome. Nat. Immunol. 18, 861–869, https://doi.org/10.1038/ni.3772

Griewankov, S.I., Greten, F.R. and Karin, M. (2010) Immunity, inflammation, and cancer. Cell, https://doi.org/10.1016/j.cell.2010.01.025

Trinchieri, G. (2012) Cancer and inflammation: an old intuition with rapidly evolving new concepts. Annu. Rev. Immunol. 30, 677–706, https://doi.org/10.1146/annurev-immunol-020711-075008

Zimbiris, C.P., Pushalakar, S., Saxena, D. and Miller, G. (2014) Pancreatic cancer, inflammation, and microbiome. Cancer J. 20, 195–202, https://doi.org/10.1097/PPO.0000000000000045

Multhoff, G., Molis, M. and Radons, J. (2011) Chronic inflammation in cancer development. Front. Immunol. 2, 98

Tafani, M., Sansone, L., Limana, F., Arcangeli, T., De Santis, E., Polese, M. et al. (2016) The interplay of reactive oxygen species, hypoxia, inflammation, and sirtuins in cancer initiation and progression. Oxid. Med. Cell Longev. 2016, 3907147, https://doi.org/10.1155/2016/3907147

Jochems, C. and Schom, J. (2011) Tumor-infiltrating immune cells and prognosis: the potential link between conventional cancer therapy and immunity. Exp. Biol. Med. 236, 567–579, https://doi.org/10.1258/ebm.2011.011007

Lewi, I., Amsalem, H., Nissan, A., Darash-Yahana, M., Perez, T., Mandelboim, O. et al. (2015) Characterization of tumor infiltrating natural killer cell subset. Oncotarget 6, 13835–13843, https://doi.org/10.18632/oncotarget.3453

Liu, Y., Tergaonkar, V., Krishna, S. and Androphy, E.J. (1999) Human papillomavirus type 16 E6-enhanced susceptibility of L929 cells to tumor necrosis factor alpha correlates with increased accumulation of reactive oxygen species. J. Biol. Chem. 274, 24819–24827, https://doi.org/10.1074/jbc.274.35.24819

Aknclair, S.C., Khattar, E., Boon, P.L.S., Unal, B., Fullwood, M.J. and Tergaonkar, V. (2016) Long-range chromatin interactions drive mutant TERT promoter activation. Cancer Discov. 6, 1276–1291, https://doi.org/10.1158/2159-8290.CD-16-0177

Li, Y., Cheng, H.S., Chng, W.J. and Tergaonkar, V. (2016) Activation of mutant TERT promoter by RAS-ERK signaling is a key step in malignant progression of BRAF-mutant human melanomas. Proc. Natl. Acad. Sci. U.S.A. 113, 14402–14407, https://doi.org/10.1073/pnas.161106113

Khattar, E., Kumar, P., Liu, C.Y., Aknclair, S.C., Raju, A., Lakshmanan, M. et al. (2016) Telomerase reverse transcriptase promotes cancer cell proliferation by augmenting RNA expression. J. Clin. Invest. 126, 4045–4060, https://doi.org/10.1172/JCI86042

Aknclair, S.C., Low, K.C., Liu, C.Y., Yan, T.D., Oji, A., Ikawa, M. et al. (2015) Quantitative assessment of telomerase components in cancer cell lines. FEBS Lett. 589, 974–984, https://doi.org/10.1016/j.febslet.2015.02.035

Apps, J.R., Carreno, G., Gonzalez-Mejia, J.M., Haston, S., Guho, R., Cooper, J.E. et al. (2018) Tumour compartment transcriptomics demonstrates the activation of inflammatory and odontogenic programmes in human adamantinomatous craniopharyngioma and identifies the MAPK/ERK pathway as a novel therapeutic target. Acta Neuropathol. 135, 757–777, https://doi.org/10.1007/s00401-018-1830-2

Janssen, L.M.E., Ramsay, E.E., Logsdon, C.D. and Overwijk, W.W. (2017) The immune system in cancer metastasis: friend or foe? J. Immunother. Cancer 5, 79, https://doi.org/10.1186/s40425-017-0283-X

Stockmann, C., Schadenhurt, D., Klooe, R. and Heftrich, I. (2014) The impact of the immune system on tumor: angiogenesis and vascular remodeling. Front. Oncol. 4, 69, https://doi.org/10.3389/fonc.2014.00069

Hoseel, B. and Schmid, J.A. (2013) The complexity of NF-κB signaling in inflammation and cancer. Mol. Cancer 12, 86, https://doi.org/10.1186/1476-4598-12-86

Dey, A., Wang, E., Kua, N., Teo, H.L., Tergaonkar, V. and Lane, D. (2008) Hexamethylene bisacetamide (HMBA) simultaneously targets AKT and MAPK pathway and represses NF kappB activity: implications for cancer therapy. Cell Cycle 7, 3759–3767, https://doi.org/10.4161/cc.7.23.7213

Tak, P.P. and Firestein, G.S. (2001) NF-kappaB: a key role in inflammatory diseases. Proc. Natl. Acad. Sci. U.S.A. 98, 14402–14407, https://doi.org/10.1073/pnas.161106113

Baker, R.G., Hayden, M.S. and Ghosh, S. (2011) NF-κB, inflammation, and metabolic disease. Mol. Cancer 10, 5257–5268, https://doi.org/10.1128/MB.24.12.5257-5268.2004

Dunleavy, K. and Wilson, W.H. (2015) Primary mediastinal B-cell lymphoma and mediastinal gray zone lymphoma: do they require a unique therapeutic approach? Blood 125, 33–39, https://doi.org/10.1182/blood-2014-05-575092
Couturier-Maillard, A., Secher, T., Rehman, A., Normand, S., De Arcangelis, A., Haesler, R. et al. (2013) NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. J. Clin. Invest. 123, 700–711

Ishaq, S. and Nunn, L. (2015) Helicobacter pylori and gastric cancer: a state of the art review. Gastroenterol. Hepatol. 8, S6–S14

Li, Z.X., Wang, Y.M., Tang, F.B., Zhang, L., Zhang, Y., Ma, J.L. et al. (2015) NOD1 and NOD2 genetic variants in association with risk of gastric cancer and its precursors in a Chinese population. PLoS ONE 10, e0124949, https://doi.org/10.1371/journal.pone.0124949

Asano, N., Imatani, A., Watanabe, T., Fushiya, J., Kondo, Y., Jin, X. et al. (2016) Cdx2 expression and intestinal metaplasia induced by H. pylori infection of gastric cells is regulated by NOD1-mediated innate immune responses. Cancer Res. 76, 1135–1145, https://doi.org/10.1158/0008-5472.CAN-15-2272

Suárez, G., Romero-Gallo, J., Piazzuolo, M.B., Wang, G., Maier, R.J., Forsberg, L.S. et al. (2015) Modulation of Helicobacter pylori peptidoglycan enhances NOD1 activation and promotes cancer of the stomach. Cancer Res. 75, 1749–1759, https://doi.org/10.1158/0008-5472.CAN-14-2291

Li, Y., Zhang, M. and Zheng, X. (2018) High expression of NLRC5 is associated with prognosis of gastric cancer. Open Med. 13, 443–449, https://doi.org/10.1515-med-2018-0066

Moossavi, M., Parsamaneh, N., Bahrami, A., Atkin, S.L. and Sahebkar, A. (2018) Role of the NLRP3 inflammasome in cancer. Mol. Cancer 17, 158, https://doi.org/10.1186/s12943-018-0900-3

Ribeiro, A.A., Costa, M.C., Alves, R.R., Villa, L.L., Saddi, V.A., Carneiro, M.A. et al. (2015) HPV infection and cervical neoplasia: associated risk factors. Infect. Agent Cancer 10, 16, https://doi.org/10.1186/s13027-015-0011-3

de Castro-Sobrinho, J.M., Rabelo-Santos, S.H., Fugueiredo-Alves, R.R., Derchain, S., Sarian, L.O., Pitta, D.R. et al. (2016) Bacterial vaginosis and inflammatory response showed association with severity of cervical neoplasia in HPV-positive women. Diagn. Cytopathol. 44, 80–86, https://doi.org/10.1002/dc.23388

Pontillo, A., Bricher, P., Leal, V.N., Lima, S., Souza, P.R. and Crowella, S. (2016) Role of inflammasome genetics in susceptibility to HPV infection and cervical cancer development. J. Med. Virol. 88, 1646–1651, https://doi.org/10.1002/jmv.24514

He, A., Shao, J., Zhang, Y., Lu, H., Wu, Z. and Xu, Y. (2017) CD200Fc reduces LPS-induced IL-1β activation in human cervical cancer cells by modulating TLR4-NF-κB and NLRP3 inflammasome pathway. Oncotarget 8, 33214–33224

Zaki, M.H., Vogel, P., Mailiredi, R.K., Body-Malapel, M., Anand, P.K., Bertin, J. et al. (2011) The NOD-like receptor NLRP12 attenuates colon inflammation and tumorigenesis. Cancer Cell 20, 649–660, https://doi.org/10.1016/j.ccr.2011.10.022

Du, Q., Wang, Q., Fan, H., Wang, J., Liu, X., Wang, H. et al. (2016) Dietary cholesterol promotes AOM-induced colorectal cancer through activating the NLRP3 inflammasome. Biochem. Pharmacol. 105, 42–54, https://doi.org/10.1016/j.bcp.2016.02.017

Liu, L., Dong, W., Wang, S., Zhang, Y., Liu, T., Xie, R. et al. (2018) Dexoycholic acid disrupts the intestinal mucosal barrier and promotes intestinal tumorigenesis. Food Funct. 9, 5588–5597, https://doi.org/10.1039/C8FO01143E

Deng, Q., Geng, Y., Zhao, L., Li, R., Zhang, Z., Li, K. et al. (2018) NLRP3 inflammasomes in macrophages drive colorectal cancer metastasis to the liver. Cancer Lett. 442, 21–30, https://doi.org/10.1016/j.canlet.2018.10.030

Zhao, Y., Guo, Q., Zhao, K., Zhou, Y., Li, W., Fan, C. et al. (2017) Small molecule GL-V9 protects against colitis-associated colorectal cancer by limiting NLRP3 inflammasome through autophagy. Oncoimmunology 7, e1375640, https://doi.org/10.1080/2162402X.2017.1375640

Wang, H., Wang, Y., Du, Q., Lu, P., Fan, H., Lu, J. et al. (2018) Inflammasome-independent NLRP3 is required for epithelial-mesenchymal transition in colon cancer cells. Exp. Cell Res. 342, 184–192, https://doi.org/10.1016/j.yexcr.2018.03.009

Zaki, M.H., Vogel, P., Body-Malapel, M., Lamkanfi, M. and Kanneganti, T.D. (2010) IL-18 production downstream of the Nlrp3 inflammasome confers protection against colorectal tumor formation. J. Immunol. 185, 4912–4920, https://doi.org/10.4049/jimmunol.1002046

Dupaul-Chicoine, J., Arabzadeh, A., Dagenais, M., Douglas, T., Champagne, C., Morìzoit, A. et al. (2015) The Nlrp3 inflammasome suppresses colorectal cancer metastatic growth in the liver by promoting natural killer cell tumoricidal activity. Immunity 43, 751–763, https://doi.org/10.1016/j.immuni.2015.08.013

Kim, J.Y., Kim, Y.M., Park, J.M., Han, Y.M., Lee, K.C., Hahm, K.B. et al. (2018) Cancer preventive effect of recombinant TRAIL by ablation of oncopgenic inflammation in colitis-associated cancer rather than anticancer effect. Oncotarget 9, 1705–1716

Amarante-Mendes, G.P. and Griffith, T.S. (2015) Therapeutic applications of TRAIL receptor agonists in cancer and beyond. Pharmacol. Ther. 155, 117–131, https://doi.org/10.1016/j.pharmthera.2015.09.001

de Miguel, D., Lemke, J., Anel, A., Walczak, H. and Martinez-Lostao, L. (2016) Onto better TRAILs for cancer treatment. Cell Death Differ. 23, 733–747, https://doi.org/10.1038/cdd.2015.174

Normand, S., Delanoye-Crespin, A., Bressenot, A., Huot, L., Grandjean, T., Peyrin-Biroulet, L. et al. (2011) Nod-like receptor pyrin domain-containing protein 6 (NLRP6) controls epithelial self-renewal and colorectal carcinogenesis upon injury. Proc. Natl. Acad. Sci. U.S.A. 108, 9601–9606, https://doi.org/10.1073/pnas.1009811810

Huber, S., Gagliani, N., Zenewicz, L.A., Huber, F.J., Bosurgi, L., Hu, B. et al. (2012) IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. Nature 491, 259–263, https://doi.org/10.1038/nature11535

Zaki, M.H., Lamkanfi, M. and Kanneganti, T.D. (2011) The Nlrp3 inflammasome: contributions to intestinal homeostasis. Trends Immunol. 32, 171–179, https://doi.org/10.1016/j.it.2011.02.002

Allen, I.C., Wilson, J.E., Schneider, M., Lich, J.D., Roberts, R.A., Arthur, J.C. et al. (2012) NLRP12 suppresses colon inflammation and tumorigenesis through the negative regulation of noncanonical NF-κB signaling. Immunity 36, 742–754, https://doi.org/10.1016/j.immuni.2012.03.012

Lortet-Tieulent, J., Ferlay, J., Bray, F. and Jemal, A. (2018) International patterns and trends in endometrial cancer incidence, 1978–2013. J. Natl. Cancer Inst. 110, 354–361, https://doi.org/10.1093/jnci/djx124

Sorosky, J.J. (2012) Endometrial cancer. Obstet. Gynecol. 120, 383–397, https://doi.org/10.1097/AOG.0b013e3182605bf1

Symons, L.K., Miller, J.E., Kay, V.R., Marks, R.M., Libilik, K., Koti, M. et al. (2018) The immunopathophysiology of endometriosis. Trends Mol. Med. 24, 748–762, https://doi.org/10.1016/j.tumor.2018.07.004
215 Ahmad, I., Muneer, K.M., Tamimi, I.A., Chang, M.E., Ata, M.O. and Yusuf, N. (2013) Thymoquinone suppresses metastasis of melanoma cells by inhibition of NLRP3 inflammasome. *Toxicol. Appl. Pharmacol.* **270**, 70–76, https://doi.org/10.1016/j.taap.2013.03.027

216 Stein, C., Caccamo, M., Laird, G. and Leptin, M. (2007) Conservation and divergence of gene families encoding components of innate immune response systems in zebrafish. *Genome Biol.* **8**, R251, https://doi.org/10.1186/gb-2007-8-11-r251

217 Zou, H., Henzel, W.J., Liu, X., Lutschg, A. and Wang, X. (1997) Apaf-1, a human protein homologous to *C. elegans* CED-4, participates in cytochrome c-dependent activation of caspase-3. *Cell* **90**, 405–413, https://doi.org/10.1016/S0092-8674(00)80501-2

218 Chereau, D., Zou, H., Spada, A.P. and Wu, J.C. (2005) A nucleotide binding site in caspase-9 regulates apoptosome activation. *Biochemistry* **44**, 4971–4976, https://doi.org/10.1021/bi047380+

219 Correa, R.G., Krajewska, M., Ware, C.F., Gerlic, M. and Reed, J.C. (2014) The NLR-related protein NWD1 is associated with prostate cancer and modulates androgen receptor signaling. *Oncotarget* **5**, 1666–1682, https://doi.org/10.18632/oncotarget.1850