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REVIEW

Epigenetic regulation of ASC/TMS1 expression: potential role in apoptosis and inflammasome function

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Abstract Cloning studies have revealed that the apoptosis-associated speck-like protein possessing a caspase-recruiting domain (ASC) and the target of methylation-induced silencing-1 (TMS) are identical proteins. ASC/TMS1 is a bipartite adaptor protein containing the N-terminal pyrin domain and the C-terminal caspase-recruitment domain. There is abundant literature on ASC/TMS1, mostly under the name TMS1, in the epigenetic regulation of apoptosis and carcinogenesis, whereas the abbreviation ASC has been adopted from studies on the assembly of inflammasomes and stimulation of inflammation. There is substantial literature emphasizing that there are common aspects in the regulation of apoptosis and inflammation, which may be related to the function of ASC/TMS1. The region of the transcription start site of *ASC/TMS1* gene contains a 600-bp-long CpG island that is highly methylated and the transcription of *ASC/TMS1* is repressed in several cancers. However, it is not known whether the ASC/TMS1-dependent epigenetic regulation controls the inflammasome functions and moreover whether this regulation has any role in the inflammation-mediated carcinogenesis or in the pathogenesis of age-related degenerative diseases. We will examine the mechanisms involved in the epigenetic regulation of ASC/TMS1 as well as their significance in the coordination of apoptosis and inflammasome functions. We will also review the role of aberrant methylation of ASC/TMS1 promoter in the function of inflammasomes, a major host defense system, in cellular housekeeping and carcinogenesis.

Keywords Ageing · Apoptosis · Epigenetics · DNA methylation · Inflammasome

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Introduction

Apoptosis is a programmed cell death mechanism that is not only activated in tissue morphogenesis during development but also in response to a variety of acute injuries and chronic degenerative diseases [1, 2]. Conversely, the repression of apoptosis can enhance carcinogenesis [3]. Recent studies have revealed that epigenetic regulation has a fundamental role in both developmental processes and cancer [4]. Apoptosis-related genes are crucial targets in the epigenetic silencing in carcinogenesis [5]. Currently, there is convincing evidence that inflammation is closely linked to carcinogenesis [6, 7]. Interestingly, both apoptosis and inflammation can be viewed as housekeeping mechanisms that maintain tissue homeostasis combating cellular damage. Inflammasomes are pattern recognition sensors for cellular stress and microbial attacks; in fact, they induce inflammatory responses that protect tissues against excessive damage [8, 9]. Since

both apoptosis and inflammasomes are guardians of tissue integrity, it is not surprising that they share some regulatory mechanisms.

In 1999, Masumoto et al. [10] cloned a novel gene translating a 22-kDa protein that formed cellular aggregates, also called specks, during apoptosis induced in HL-60 cells by retinoic acid and etoposide. They termed this gene *apoptosis-associated speck-like protein containing a caspase-recruiting domain (ASC)*. Independently, Conway et al. [11] were investigating the genes silenced by the overexpression of DNA methyltransferase, which could induce the aberrant DNA methylation in CpG islands, a feature commonly observed in cancer cells. They cloned the gene which they termed the *target of methylation-induced silencing-1* (*TMS1*). Interestingly, the *ASC* and *TMS1* turned out to be an identical gene, which was later also termed as *PYCARD* since it is a bipartite protein containing both the N-terminal pyrin domain (PYD) and the C-terminal caspase-recruitment domain (CARD) [8, 9, 12]. ASC/TMS1 is an important adaptor protein interacting with caspases via the CARD domain and inflammasome receptors via the PYD domain. Unfortunately, there is no consensus in the literature about the name; TMS1 has commonly been applied in the cancer studies on the epigenetic regulation of apoptosis, whereas ASC is used in the studies on inflammasome assembly and pyroptosis. In this review, we will examine the significance of epigenetic regulation of ASC/TMS1 adaptor in the coordinated functions of apoptosis and inflammasomes. Moreover, we will review evidence indicating that the aberrant methylation of CpG island of ASC/TMS1 might suppress the function of inflammasomes in cancer cells and thus disturb housekeeping and promote carcinogenesis.

Biology of ASC/TMS1

Epigenetic regulation of *ASC/TMS1* expression

The epigenetic regulation of gene expression is controlled by DNA and histone methylation [13, 14]. This methylomics organizes the chromatin structure; open chromatin activates transcription, whereas closed chromatin silences gene expression. CpG islands are specific genomic loci that are rich in CpG sites, locating especially in the promoters of housekeeping genes [15]. CpG islands are normally unmethylated targeting transcription factors that stimulate gene transcription. There are several mechanisms that can maintain CpG islands unmethylated or enhance their methylation by DNA methyltransferases [14–16]. Moreover, there is a close crosstalk between histone methylation and DNA methylation in the control of gene transcription in a distinct DNA locus [13, 16].

The cloning experiments revealed that there is a 600-bp-long CpG island in the region of transcription start site of the *ASC/TMS1* gene [17]. Several studies have demonstrated that the methylation status of this CpG island correlates with the expression level of ASC/TMS1, i.e., the unmethylated CpG locus represents the active transcription of *ASC/TMS1*, whereas hypermethylated locus denotes an inactive state, as is observed in many cancer cells [11, 17, 18]. The group of Prof. Paula Vertino has probed the role of epigenetic regulation in the expression of *ASC/TMS1* gene [19–21]. In the control cells expressing *ASC/TMS1*, the unmethylated CpG island is surrounded by the flanking regions, which are extensively methylated. In the active state, the unmethylated CpG island contains three DNase I-hypersensitive sites but no nucleosomes [17]. Lucas et al. [20] demonstrated that GA-binding proteins (GABPα and GABPβ) assembled heteromeric complexes in the unmethylated CpG region. They also observed that the occupancy of GABP complexes prevented the methylation of the CpG island and thus enhanced the expression of *ASC/TMS1* gene. The 5′ end flanking domain of CpG region was marked by histone H3K4 methylation and positioned with the nucleosomes [19]. Moreover, this flanking site contained a dense acetylation of H4K16, which was induced by the histone acetyltransferase, hMOF. Recently, Kapoor-Vazirani et al. [21] demonstrated that the methyltransferase SUV420H2 trimethylated H4K20, which induced the promoter-proximal pausing of RNA polymerase II (Pol II), whereas the hMOF-mediated H4K16 acetylation activated the transcription by releasing the pausing of Pol II. The promoter-proximal pausing of Pol II is a common mechanism to control the early elongation, particularly at genes under signal-responsive regulation [22]. These studies indicated that the hMOF-induced H4K16 acetylation and SUV420H2-mediated H4K20 trimethylation exert antagonistic roles in the control of *ASC/TMS1* transcription.

The aberrant methylation of CpG island of *ASC/TMS1* in cancer cells was associated with (a) a decrease in the level of methylated H3K4 and acetylated H4K16, (b) an increase in the methylation of H3K9, and (c) a loss of nucleosome positioning [19]. Moreover, the methylation of CpG island repressed the recruitment of Pol II to the promoter of *ASC/TMS1* and thus silenced transcription [21]. It is well known that the methylation of H3K4 in gene promoter regions is an epigenetic mark for transcriptional activation, whereas the methylation of H3K9 and H4K20 are common repressive sites [23]. In particular, the unmodified H3K4 can bind DNA methyltransferase (DNMT3), which can enhance the methylation of CpG sites, whereas methylated H3K4 can interact with proteins preventing the methylation of CpG island [16]. Moreover, the methylation of H3K9 is commonly linked to the methylation of nearby CpG sites [16, 24]. On the other hand, Kagey et al. [25] demonstrated

that the transient exposure to 5-aza-2′-deoxycytidine, a common DNA methyltransferase inhibitor, enhanced the demethylation of CpG island, which was associated with a reduced level of repressive chromatin marks, such as H3K9me2 and H4K20me3, and increased the recruitment of Pol II to the ASC/TMS1 locus [25]. All these studies clearly indicated that the transcription of *ASC/TMS1* gene is under epigenetic control.

Role of ASC/TMS1 in apoptosis and carcinogenesis

Cloning studies already revealed that the *ASC/TMS1* gene regulates apoptosis via the CARD domain [10, 11]. Subsequently, a plethora of clinical studies have demonstrated that the CpG island is aberrantly hypermethylated in several cancers implying that *ASC/TMS1* gene is a tumor suppressor gene [26]. For instance, there are reports that the *ASC/TMS1* gene is hypermethylated in breast and lung cancers [11, 27], melanoma [28], prostate cancer [29, 30], glioblastoma multiforme [31, 32], and neuroblastoma [33]. The increased methylation level is commonly associated with the decreased expression of the *ASC/TMS1* gene. Moreover, the exposure of cancer cells to DNA methyltransferase inhibitors, such as 5-aza-2′-deoxycytidine and zebularine, could restore the expression of ASC/TMS1 and induce apoptosis [18, 29–31]. In addition, two histone deacetylase inhibitors, trichostatin A and sodium butyrate, were also able to re-establish the expression of ASC/TMS1 in cancer cells [34, 35]. The methylation status of the CpG island of *ASC/TMS* gene is generally a sensitive prognostic marker for tumorigenesis. Given that ASC/TMS1 is a proapoptotic protein, the epigenetic inhibition of *ASC/TMS1* gene in cancer cells renders them resistant to apoptotic cell death. However, ASC/TMS1 knockout mice have not revealed spontaneous tumorigenesis although they lack the expression of ASC/TMS1. Interestingly, Drexler et al. [36] demonstrated that the conditional knockout of ASC/TMS1 in keratinocytes or bone marrow-derived macrophages provoked the DMBA/TPA-induced tumorigenesis in keratinocytes but suppressed tumor formation in myeloid cells. They speculated that the tissue-specific responses could explain the absence of tumors in ASC/TMS1 knockout mice.

Currently, the exact mechanism through which ASC/TMS1 induces apoptosis is still unclear. Ohtsuka et al. [37] demonstrated that ASC/TMS1 could interact with BAX, a pro-apoptotic protein that induced apoptosis via the mitochondrial pathway (Fig. 1). They observed that BAX protein could bind to the PYD domain of ASC/TMS1. Interestingly, they revealed that ASC/TMS1 acted as a carrier protein of BAX by translocating it to mitochondria. However, a recent study has claimed that the BAX-dependent apoptosis could be linked to the activation of caspase-8

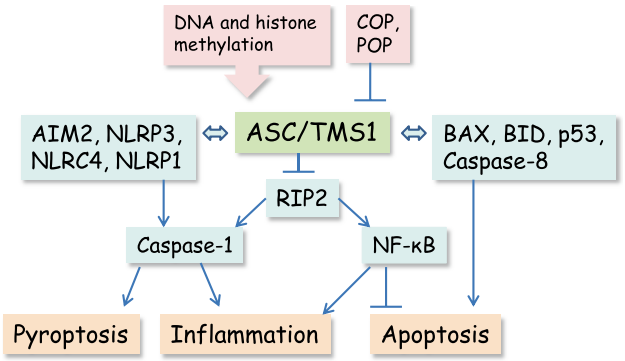

Fig. 1 Epigenetic regulation of ASC/TMS1 expression affects its interaction with inflammasome receptors and apoptosis-inducing proteins. ASC/TMS1 assembles the inflammasome complexes with AIM2, NLRP3, NLRC4, and NLRP1 receptors. These complexes activate caspase-1, which subsequently stimulates inflammatory responses. ASC/TMS1 inhibits RIP2 kinase, which context-dependently can control apoptosis and inflammation via the activation of NF-κB and caspase-1. In addition, ASC/TMS1 can interact with apoptosis-inducing BAX, BID, p53, and caspase-8 proteins and directly enhance apoptosis. COP and POP proteins inhibit the function of ASC/TMS1

[38]. It was also demonstrated that ASC/TMS1 can interact with caspase-8 [39], in addition to the well-known inflammatory caspase-1 and caspase-5 [40, 41]. Masumoto et al. [39] observed that ASC/TMS1 interacted with caspase-8 in the ternary complex containing also NOD-like receptor NLRC4. The lack of caspase-8 rescued fibroblasts from the ASC/TMS1-induced apoptosis which indicated that caspase-8, an initiator caspase, probably could stimulate effector caspase-mediated apoptosis. Hasegawa et al. [38] reported that the ASC/TMS1-mediated apoptosis was also activated by the caspase-8-induced proteolytic maturation of BID protein. The pro-apoptotic BID could trigger the death receptor-activated, mitochondria-mediated apoptotic pathway [42]. However, there does seem to be cell-type-specific differences in caspase-8-linked, ASC/TMS1-enhanced apoptosis [38, 43]. Recently, Drexler et al. [36] demonstrated that ASC/TMS1 could display cell-type-specific functions, i.e., it has a proinflammatory role in myeloid cells whereas in epidermal keratinocytes, ASC/TMS1 acts as a tumor suppressor, probably in association with p53 activation (Fig. 1). These workers reported that UVB treatment of keratinocytes promoted a transient interaction between ASC/TMS1 and p53. The lack of ASC/TMS1 reduced the phosphorylation of p53 and subsequently decreased the expression of its target genes. It is well known that the p53 protein is a potent inducer of apoptosis [44] and thus ASC/TMS1 could potentiate the p53-dependent apoptosis. These studies imply that the reduced expression of ASC/TMS1 in cancer cells can block apoptotic cell death and enhance carcinogenesis.

Recently, Liu et al. [45] demonstrated that the expression of ASC/TMS1 inhibited NF-κB activity in primary melanoma cells, whereas the forced expression of ASC/TMS1 in metastatic melanoma, cells that are normally deficient in ASC/TMS1, enhanced NF-κB activity and potentiated tumorigenesis. ASC/TMS1 has several interacting proteins containing either CARD or PYD domains [26]. For instance, receptor interacting protein-2 (RIP2) contains a CARD domain [46], as well as caspase-1 [40, 41]. It is known that RIP2 is a potent enhancer of NF-κB activation [47]. Lamkanfi et al. [48] demonstrated that caspase-1 interacted with RIP2 and RIP-2-dependently it activated NF-κB. This activation was not dependent on the activity of caspase-1. Later, Sarkar et al. [49] observed that ASC/TMS1 is an inhibitor of RIP2-mediated NF-κB activation in HEK293 cells (Fig. 1). They also reported that the suppression of ASC/TMS1 expression dose-dependently enhanced NF-κB activation but simultaneously reduced IL-1β processing, evidence for the inhibition of caspase-1-dependent inflammasomes. A recent study revealed that ASC/TMS1 could context-dependently regulate the formation of inflammasome complexes or RIP2-dependent NF-κB activation [50]. Moreover, Hasegawa et al. [51] demonstrated that caspase-8 was also able to control the ASC/TMS1-mediated NF-κB activation. In conclusion, it seems that the balance between the ASC/TMS1-mediated apoptotic and inflammatory responses is under the context-dependent regulation of the complex formation between CARD and PYD domain-containing proteins, which subsequently process the specific downstream target proteins to trigger distinct cellular functions. The suppression of ASC/TMS1 expression, a phenomenon frequently observed in cancer cells, inhibits apoptosis but on the other hand, it can enhance NF-κB-dependent inflammatory responses.

Role of ASC/TMS1 in inflammasome assembly and pyroptosis

In their seminal study, Martinon et al. [40] demonstrated that ASC/TMS1 is an adaptor protein in the assembly of inflammasomes, which are key players in innate immunity defense. Inflammasomes are molecular platforms containing a pattern recognition receptor protein that recruits the inflammatory caspases, especially caspase-1, to trigger the processing of pro-IL-1β and pro-IL-18 into mature cytokines capable to stimulate inflammatory responses [8, 12, 52, 53]. NOD-like receptors (NLR), especially NLRP3, are the major guardians of tissue homeostasis and defense system against microbial attack. NLRP3 can be activated by a large variety of pathogens and cellular stress insults, generally called danger-associated molecular patterns (DAMPs). Absent in melanoma-2 (AIM2) receptors recognize specifically microbial DNA as well as cellular DNA relocated into the cytoplasm [54, 55]. In addition, NLRP1 and NLRC4 (also known as IPAF or CARD12) activate caspase-1 via ASC/TMS1 adaptor protein [40, 56, 57]. In general, NLRs bind caspase-1 directly via the CARD domains but NLRP1, NLRP3, and AIM2 do not contain CARD domain, instead they bind via the PYD domain to the ASC/TMS1 adaptor, which subsequently interacts with caspase-1 through its CARD domains [12, 40]. Although NLRC4 contains a CARD domain, its activation becomes enhanced in the presence of ASC/TMS1 [56]. ASC/TMS1 probably binds to the CARD domain of NLRC4 potentiating the activation [52, 57]. These studies indicate that ASC/TMS1 has a crucial role in the assembly and activation of AIM2, NLRP1, NLRP3, and NLRC4 inflammasomes in the stimulation of inflammatory responses (Fig. 1). The priming of inflammasomes [9] involves an increased expression of proforms of IL-1β and IL-18 and commonly also that of inflammasomal receptors, such as NLRP3 [58] and AIM2 [59, 60] in inflammatory conditions.

The mechanisms involved in the activation of NLRP3 and AIM2 have recently been the focus of inflammation research and there are several detailed reviews on that topic [8, 9, 12, 61]. Oxidative stress, lysosomal destabilization, potassium efflux, crystals, and protein aggregates are common endogenous inducers of NLRP3 inflammasomes. Moreover, NLRP3/ASC inflammasomes can be activated by high levels of saturated fatty acids [62], which indicates that NLRP3 inflammasomes have a key role in the pathogenesis of the metabolic syndrome [63, 64]. The aging process also involves stress components associated with the activation of NLRP3 inflammasomes [65]. The drug discovery programs for inflammasome inhibition, so-called inflammasome blockers, are still at the early phase of development [66]. However, it may be challenging to find specific targets since the ASC/TMS1 adaptor protein is involved in different pathways and side effects could be the problem. There are several endogenous proteins that can inhibit the function of ASC/TMS1. These are CARD-only (COPs) and PYD-only (POPs) proteins that bind to the CARD or PYD domains, inhibiting the assembly of inflammasomes [67] (Fig. 1). In addition to endogenous proteins, some viral proteins also target themselves to ASC/TMS1 in order to inhibit the function of NLRP3 and AIM2 [68].

Pyroptosis is a caspase 1-dependent, cell death mechanism that can be stimulated by many pathological insults, e.g., microbial infections and tissue injuries [69]. Apoptosis and pyroptosis are analogous cell death mechanisms but they display several fundamental differences, e.g., (a) pyroptosis enhances the inflammatory response, while apoptosis does not induce inflammation, (b) pyroptosis causes membrane swelling and rupture whereas apoptosis triggers the formation of apoptotic bodies, (c) pyroptosis is an exclusively caspase-1-dependent process, whereas

apoptosis is associated with other caspases, e.g., 2, 3, and 6–10. Moreover, ASC/TMS1 has a major role in the formation of pyroptosomes, large supramolecular assemblies containing ASC/TMS1 and caspase-1 proteins [70]. Fernandes-Alnemri et al. [70] demonstrated that pyroptosomes are formed by the dimerization of ASC/TMS1 via the PYD domains, whereas the CARD domains recruit procaspase-1. They revealed that the stimulation of THP-1 macrophages by several pro-inflammatory stimuli triggered the formation of large aggregate-like structures, i.e., ASC/TMS1 specks, usually with one pyroptosome in each cell. Cheng et al. [71] have described in detail the dynamics of the speck formation in epithelial cells. The specks are protein aggregates that trigger the caspase-1-mediated pyroptotic cell death [70]. Recent studies have demonstrated that the activation of NLRP3 and AIM2 receptors can also lead to pyroptosis if the stimulus is strong enough [72, 73]. Moreover, pyroptosis can be induced without speck formation [73, 74]. Interestingly, there are also studies revealing that the activation of AIM2 and NLRP3 inflammasomes can recruit procaspase-8, instead of procaspase-1, via ASC/TMS1 and consequently trigger apoptosis [75, 76].

ASC/TMS1 can also increase the expression level of Dock2 by stabilizing its mRNA [77]. This inflammasome-independent response potentiates the Rac activation and actin polymerization in lymphocytes, which enhances their chemotaxis and migration. It seems that ASC/TMS1 also controls antigen uptake and presentation in dendritic cells [77]. However, later studies revealed that the $ASC^{-/-}$ mice were also defective in Dock2 expression, and thus it seems that ASC/TMS1 does not regulate adaptive immunity responses via Dock2 pathway [78].

Significance of epigenetic regulation of ASC/TMS1

As described earlier, the *ASC/TMS1* gene is a sensitive target of DNA methylation in different types of cancers, thus suppressing apoptotic cell death of cancerous cells. It is known that the demethylation of the *ASC/TMS1* gene can sensitize cancer cells for stimuli, which induce apoptosis through p53 and TRAIL activation [79, 80]. Nakajima et al. [81] demonstrated that the aging process decreased the methylation status of CpG island in the *ASC/TMS1* gene, which implies that the expression of ASC/TMS1 might be elevated during aging enhancing sensitivity to inflammasome activation and inflammatory responses with aging. It is known that the aging process is associated with a global genome-wide hypomethylation of DNA, a hallmark of the aging process [82]. Nakajima et al. [81] reported that physical exercise elevated the methylation level of *ASC/TMS1* gene in human peripheral blood, probably by decreasing the sensitivity to inflammatory reactions following an exercise training program. Moreover, Youm et al. [83] observed that the knockout of the *ASC/TMS1* gene protected mouse thymus against the age-related decline in thymic mass and cellularity, most likely by reducing apoptosis and inflammation. These observations indicate that the modulation of ASC/TMS1 expression, probably via epigenetic control, has a crucial role in the regulation of apoptosis and inflammation.

ASC/TMS1 coordinates apoptosis and inflammasome functions

Given that apoptosis and inflammation are important host defense mechanisms [84, 85], it is not surprising that their regulation is coordinated by a common adaptor protein, ASC/TMS1. Although the ASC/TMS1-mediated pathways represent only one component of the complex regulation of apoptosis and inflammation, they are specifically under epigenetic regulation. The coordinated function of inflammasomes and apoptosis confers significant benefits in the maintenance of tissue homeostasis in pathological conditions (Fig. 2). Inflammasomes are sensitive at sensing insults jeopardizing cellular housekeeping, and subsequently they can trigger the secretion of cytokines and chemokines able to recruit phagocytes to the threatened tissue. The appearance of phagocytes potentiates the clearance of apoptotic bodies generated by apoptotic cell death. However, the overwhelming expression of ASC/TMS1 and inflammasome activation can lead to pyroptosis. Several studies have revealed that the expression of ASC/TMS1, in addition to NLRP3, is substantially increased in pathological conditions, e.g., after brain injuries [86], atherosclerosis [87], and infections [88]. Currently, it is well known that the expression of the *ASC/TMS1* gene is epigenetically regulated in cancer but the role of DNA methylation of *ASC/TMS1* in inflammatory diseases still needs to be clarified. However, a high-fat diet for over three generations induced the DNA hypomethylation of several inflammatory genes, increased their expression, and maintained chronic inflammation in mouse adipose tissue [89]. On the other hand, the ASC/TMS1-mediated coordination of apoptosis and inflammasome functions is limited to the cells where both ASC/TMS1 and inflammasome receptors are expressed. NLRP3 and AIM2 are mostly expressed in innate immunity and epithelial cells [59, 60, 90] but NLRP1 can also be expressed in many other tissues, e.g., in neurons [90]. Moreover, it is known that the infiltrating macrophages have a crucial role in the pathogenesis of obesity and metabolic syndrome [91]. Stienstra et al. [92] demonstrated that high-fat diet (HFD)-induced obesity was prevented in NLRP3 knockout mice. Interestingly, they also reported that HFD did not induce insulin resistance, liver steatosis, or adipocyte hypertrophy in ASC/TMS1-depleted mice.

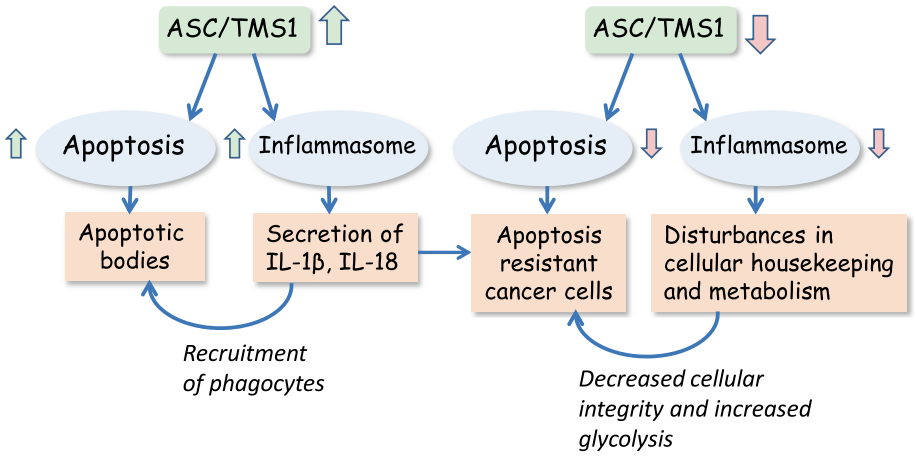

Fig. 2 The expression of ASC/TMS1 coordinates the function of apoptosis and inflammasomes in carcinogenesis. The upregulation of ASC/TMS1 expression enhances apoptosis and the assembly of inflammasomes. The activation of inflammasomes induces the secretion of IL-1β and IL-18, which provoke an inflammatory response but also stimulate the recruitment of phagocytes into the tissues to clear the apoptotic bodies produced by apoptotic cell death. Increased sensitivity to apoptosis and effective clearance of apoptotic bodies prevent carcinogenesis. On the other hand, chronic inflammatory environment can enhance carcinogenesis, e.g., via reactive oxygen species and many cytokines and chemokines, which is not directly linked to the activation of inflammasomes. The epigenetic inhibition of ASC/TMS1 expression, observed in many cancers, inhibits apoptosis and exposes cells to excessive proliferation. The lack of expression of ASC/TMS1 represses the function of AIM2 and NLRP3 inflammasomes, which leads to disturbances in cellular housekeeping, e.g., pathogen recognition, and, moreover, a deficiency of caspase-1 activation can increase the level of glycolytic enzymes, which are degraded by caspase-1. Decreased cellular integrity and increased glycolytic metabolism are the hallmarks of apoptosis-resistant cancer cells. This figure is a hypothetical presentation and there can be cell type differences in the response to deficiency of ASC/TMS1 expression, as described by Drexler et al. [36] and discussed in the text

This indicates that the function of ASC/TMS1 in invading inflammatory cells has a fundamental role in many diseases, although it is not expressed in target tissue cells.

In physiological terms, it seems quite logical that the regulation of apoptosis and inflammasome function would be linked to DNA methylation. For instance, apoptosis, i.e., programmed cell death, is an important mechanism deciding the fate of the cell during morphogenesis. Given that DNA methylation is the mechanism that controls the differentiation of cells into specific tissues [93], a lack of methylation could stimulate the apoptosis of cells superfluous to tissue development. The cleansing of cell debris via the inflammasome-induced recruitment of phagocytes could prevent chronic inflammation (Fig. 2). On the other hand, the genome-wide changes in DNA methylation, observed in the aging process [94, 95], could provoke the ASC/TMS1-mediated apoptosis and impaired inflammasome function, even pyroptosis. Interestingly, epigenetic regulation could determine the fate of distinct cells in tissues via ASC/TMS1 activation, both during development and under pathological conditions, without disturbing tissue homeostasis.

Role of inflammasomes in carcinogenesis

There is abundant literature indicating that inflammation can enhance carcinogenesis [6, 96]. However, the ASC/TMS1-mediated activation of inflammasome seems to have context-dependent, opposite effects on carcinogenesis, as recently reviewed [97, 98]. The activation of inflammasomes stimulates IL-1β and IL-18 secretion, which provokes inflammatory response, e.g., by recruiting phagocytes to damaged tissue and thus enhancing the cleansing of apoptotic bodies and cell debries (Fig. 2). This inflammatory response also involves the generation of many factors, e.g., reactive oxygen species and many cytokines and chemokines, which are associated with cancer formation [6, 96]. Given that inflammasome receptors are highly expressed in several chronic inflammatory diseases, e.g., psoriasis [59] and atherosclerosis [60], which are not linked to tumorigenesis, it seems that the activation of inflammasomes do not directly induce tumor formation.

There are several studies indicating that NLRP3 inflammasomes can inhibit tumorigenesis, e.g., during chronic intestinal inflammation [99, 100]. Zaki et al. [101] demonstrated that IL-18 conferred protection against colitis-induced tumorigenesis by activating IFN-γ production. Subsequently, IFN-γ induced the STAT1-dependent tumor suppressor pathway. Allen et al. [99] observed that the presence of ASC/TMS1 and caspase-1 were required for tumor prevention in experimentally induced colitis. Many reports have revealed that the lack of ASC/TMS1 enhances tumor formation in different experimental models [36, 45, 99]. Drexel et al. [36] reported that ASC/TMS1-induced

tumor suppression was associated with p53 activation. It is also known that the inhibition of ASC/TMS1 expression can increase NF-κB signaling [49], a prominent inducer of apoptotic resistance [102]. The activation of NF-κB signaling also stimulates inflammatory responses and thus could provoke the inflammation present in cancers. The deficient expression of the ASC/TMS1 protein may also jeopardize the cellular housekeeping and disturb the control of cell integrity, which enhances the apoptotic resistance commonly encountered in cancer cells (Fig. 2). Moreover, caspase-1 has many inflammation-independent targets, such as the glycolytic enzymes [103]. Therefore, the lack of ASC/TMS1 can increase the cellular glycolytic rate, which is significantly increased in cancer cells. It seems that inflammasomes have a crucial role in the defense against carcinogenesis and thus increased methylation of the CpG island of *ASC/TMS1* gene can promote carcinogenesis.

Conclusions

ASC/TMS1 is an important adaptor protein since it can interact with several proapoptotic proteins as well as AIM2 and NLRP3 inflammasome receptors. Many context-dependent factors coordinate these distinct functions of ASC/TMS1 in cellular housekeeping. The promoter region of *ASC/TMS1* gene contains a CpG island, a feature commonly present in housekeeping genes. Several reports have demonstrated that the level of CpG island methylation correlated with the degree of ASC/TMS1 expression. With the CpG island being highly methylated, the expression of ASC/TMS1 was blocked in many cancers. Demethylation enhanced the expression of ASC/TMS1 and induced apoptosis in cancer cells. These studies have convincingly indicated that the level of DNA methylation is a major mechanism controlling the expression of ASC/TMS1 and thus it is under complex epigenetic regulation. DNA methylation is a crucial mechanism in carcinogenesis, e.g., methylation leads to the inhibition of tumor suppressor genes. However, currently it is still unknown whether epigenetic mechanisms control the function of inflammasomes and thus inflammatory responses. Given that aging and many nutritional and environmental factors affect the DNA methylation status, it seems that the epigenetic regulation of ASC/TMS1 exerts fundamental effects not only on carcinogenesis but on the pathogenesis of many age-related diseases, which are associated with apoptotic and inflammatory components.

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References

1. Conradt B (2009) Genetic control of programmed cell death during animal development. Annu Rev Genet 43:493–523
2. Zhivotovsky B, Orrenius S (2010) Cell death mechanisms: cross-talk and role in disease. Exp Cell Res 316:1374–1383
3. Fulda S (2009) Tumor resistance to apoptosis. Int J Cancer 124:511–515
4. Jones PA, Baylin SB (2007) The epigenomics of cancer. Cell 128:683–692
5. Murphy TM, Perry AS, Lawler M (2008) The emergence of DNA methylation as a key modulator of aberrant cell death in prostate cancer. Endocr Relat Cancer 15:11–25
6. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G (2006) Inflammation and cancer: how hot is the link? Biochem Pharmacol 72:1605–1621
7. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell 140:883–899
8. Davis BK, Wen H, Ting JP (2011) The inflammasome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol 29:707–735
9. Latz E, Xiao TS, Stutz A (2013) Activation and regulation of the inflammasomes. Nat Rev Immunol 13:397–411
10. Masumoto J, Taniguchi S, Ayukawa K, Sarvotham H, Kishino T, Niikawa N, Hidaka E, Katsuyama T, Higuchi T, Sagara J (1999) ASC, a novel 22-kDa protein, aggregates during apoptosis of human promyelocytic leukemia HL-60 cells. J Biol Chem 274:33835–33838
11. Conway KE, McConnell BB, Bowring CE, Donald CD, Warren ST, Vertino PM (2000) TMS1, a novel proapoptotic caspase recruitment domain protein, is a target of methylation-induced gene silencing in human breast cancers. Cancer Res 60:6236–6242
12. Schroder K, Tschopp J (2010) The inflammasomes. Cell 140:821–832
13. Cedar H, Bergman Y (2009) Linking DNA methylation and histone modification: patterns and paradigms. Nat Rev Genet 10:295–304
14. Jones PA (2012) Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat Rev Genet 13:484–492
15. Deaton AM, Bird A (2011) CpG islands and the regulation of transcription. Genes Dev 25:1010–1022
16. Hashimoto H, Vertino PM, Cheng X (2010) Molecular coupling of DNA methylation and histone methylation. Epigenomics 2:657–669
17. Stimson KM, Vertino PM (2002) Methylation-mediated silencing of TMS1/ASC is accompanied by histone hypoacetylation and CpG island-localized changes in chromatin architecture. J Biol Chem 277:4951–4958
18. Levine JJ, Stimson-Crider KM, Vertino PM (2003) Effects of methylation on expression of TMS1/ASC in human breast cancer cells. Oncogene 22:3475–3488
19. Kapoor-Vazirani P, Kagey JD, Powell DR, Vertino PM (2008) Role of hMOF-dependent histone H4 lysine 16 acetylation in the maintenance of TMS1/ASC gene activity. Cancer Res 68:6810–6821
20. Lucas ME, Crider KS, Powell DR, Kapoor-Vazirani P, Vertino PM (2009) Methylation-sensitive regulation of TMS1/ASC by the Ets factor, GA-binding protein-α. J Biol Chem 284:14698–14709
21. Kapoor-Vazirani P, Kagey JD, Vertino PM (2011) SUV420H2-mediated H4K20 trimethylation enforces RNA polymerase II promoter-proximal pausing by blocking hMOF-dependent H4K16 acetylation. Mol Cell Biol 31:1594–1609
22. Adelman K, Lis JT (2012) Promoter-proximal pausing of RNA polymerase II: emerging roles in metazoans. Nat Rev Genet 13:720–731

23. Scharf AN, Imhof A (2011) Every methyl counts–epigenetic calculus. FEBS Lett 585:2001–2007
24. Chang Y, Sun L, Kokura K, Horton JR, Fukuda M, Espejo A, Izumi V, Koomen JM, Bedford MT, Zhang X, Shinkai Y, Fang J, Cheng X (2011) MPP8 mediates the interactions between DNA methyltransferase Dnmt3a and H3K9 methyltransferase GLP/G9a. Nat Commun 2:533
25. Kagey JD, Kapoor-Vazirani P, McCabe MT, Powell DR, Vertino PM (2010) Long-term stability of demethylation after transient exposure to 5-aza-2′-deoxycytidine correlates with sustained RNA polymerase II occupancy. Mol Cancer Res 8:1048–1059
26. McConnell BB, Vertino PM (2004) TMS1/ASC: the cancer connection. Apoptosis 9:5–18
27. Virmani A, Rathi A, Sugio K, Sathyanarayana UG, Toyooka S, Kischel FC, Tonk V, Padar A, Takahashi T, Roth JA, Euhus DM, Minna JD, Gazdar AF (2003) Aberrant methylation of TMS1 in small cell, non small cell lung cancer and breast cancer. Int J Cancer 106:198–204
28. Guan X, Sagara J, Yokoyama T, Koganehira Y, Oguchi M, Saida T, Taniguchi S (2003) ASC/TMS1, a caspase-1 activating adaptor, is downregulated by aberrant methylation in human melanoma. Int J Cancer 107:202–208
29. Collard RL, Harya NS, Monzon FA, Maier CE, O'Keefe DS (2006) Methylation of the ASC gene promoter is associated with aggressive prostate cancer. Prostate 66:687–695
30. Das PM, Ramachandran K, Vanwert J, Ferdinand L, Gopisetty G, Reis IM, Singal R (2006) Methylation mediated silencing of TMS1/ASC gene in prostate cancer. Mol Cancer 5:28
31. Stone AR, Bobo W, Brat DJ, Devi NS, Van Meir EG, Vertino PM (2004) Aberrant methylation and down-regulation of TMS1/ASC in human glioblastoma. Am J Pathol 165:1151–1161
32. Martinez R, Schackert G, Esteller M (2007) Hypermethylation of the proapoptotic gene TMS1/ASC: prognostic importance in glioblastoma multiforme. J Neurooncol 82:133–139
33. Grau E, Martinez F, Orellana C, Canete A, Yanez Y, Oltra S, Noguera R, Hernandez M, Bermudez JD, Castel V (2011) Hypermethylation of apoptotic genes as independent prognostic factor in neuroblastoma disease. Mol Carcinog 50:153–162
34. Zhang C, Li H, Zhou G, Zhang Q, Zhang T, Li J, Zhang J, Hou J, Liew CT, Yin D (2007) Transcriptional silencing of the TMS1/ASC tumour suppressor gene by an epigenetic mechanism in hepatocellular carcinoma cells. J Pathol 212:134–142
35. Zhang S, Bai J, Ren S, Wang R, Zhang L, Zuo Y (2012) Sodium butyrate restores ASC expression and induces apoptosis in LS174T cells. Int J Mol Med 30:1431–1437
36. Drexler SK, Bonsignore L, Masin M, Tardivel A, Jackstadt R, Hermeking H, Schneider P, Gross O, Tschopp J, Yazdi AS (2012) Tissue-specific opposing functions of the inflammasome adaptor ASC in the regulation of epithelial skin carcinogenesis. Proc Natl Acad Sci USA 109:18384–18389
37. Ohtsuka T, Ryu H, Minamishima YA, Macip S, Sagara J, Nakayama KI, Aaronson SA, Lee SW (2004) ASC is a Bax adaptor and regulates the p53-Bax mitochondrial apoptosis pathway. Nat Cell Biol 6:121–128
38. Hasegawa M, Kawase K, Inohara N, Imamura R, Yeh WC, Kinoshita T, Suda T (2007) Mechanism of ASC-mediated apoptosis: bid-dependent apoptosis in type II cells. Oncogene 26:1748–1756
39. Masumoto J, Dowds TA, Schaner P, Chen FF, Ogura Y, Li M, Zhu L, Katsuyama T, Sagara J, Taniguchi S, Gumucio DL, Nunez G, Inohara N (2003) ASC is an activating adaptor for NF-κB and caspase-8-dependent apoptosis. Biochem Biophys Res Commun 303:69–73
40. Martinon F, Burns K, Tschopp J (2002) The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell 10:417–426
41. Srinivasula SM, Poyet JL, Razmara M, Datta P, Zhang Z, Alnemri ES (2002) The PYRIN-CARD protein ASC is an activating adaptor for caspase-1. J Biol Chem 277:21119–21122
42. Kantari C, Walczak H (2011) Caspase-8 and bid: caught in the act between death receptors and mitochondria. Biochim Biophys Acta 1813:558–563
43. Motani K, Kawase K, Imamura R, Kinoshita T, Kushiyama H, Suda T (2010) Activation of ASC induces apoptosis or necrosis, depending on the cell type, and causes tumor eradication. Cancer Sci 101:1822–1827
44. Fridman JS, Lowe SW (2003) Control of apoptosis by p53. Oncogene 22:9030–9040
45. Liu W, Luo Y, Dunn JH, Norris DA, Dinarello CA, Fujita M (2013) Dual role of apoptosis-associated speck-like protein containing a CARD (ASC) in tumorigenesis of human melanoma. J Invest Dermatol 133:518–527
46. Meylan E, Tschopp J (2005) The RIP kinases: crucial integrators of cellular stress. Trends Biochem Sci 30:151–159
47. McCarthy JV, Ni J, Dixit VM (1998) RIP2 is a novel NF-κB-activating and cell death-inducing kinase. J Biol Chem 273:16968–16975
48. Lamkanfi M, Kalai M, Saelens X, Declercq W, Vandenabeele P (2004) Caspase-1 activates nuclear factor of the κ-enhancer in B cells independently of its enzymatic activity. J Biol Chem 279:24785–24793
49. Sarkar A, Duncan M, Hart J, Hertlein E, Guttridge DC, Wewers MD (2006) ASC directs NF-κB activation by regulating receptor interacting protein-2 (RIP2) caspase-1 interactions. J Immunol 176:4979–4986
50. Kersse K, Lamkanfi M, Bertrand MJ, Vanden Berghe T, Vandenabeele P (2011) Interaction patches of procaspase-1 caspase recruitment domains (CARDs) are differently involved in procaspase-1 activation and receptor-interacting protein 2 (RIP2)-dependent nuclear factor κB signaling. J Biol Chem 286:35874–35882
51. Hasegawa M, Imamura R, Kinoshita T, Matsumoto N, Masumoto J, Inohara N, Suda T (2005) ASC-mediated NF-κB activation leading to interleukin-8 production requires caspase-8 and is inhibited by CLARP. J Biol Chem 280:15122–15130
52. Lamkanfi M, Dixit VM (2009) Inflammasomes: guardians of cytosolic sanctity. Immunol Rev 227:95–105
53. Martinon F, Mayor A, Tschopp J (2009) The inflammasomes: guardians of the body. Annu Rev Immunol 27:229–265
54. Schattgen SA, Fitzgerald KA (2011) The PYHIN protein family as mediators of host defenses. Immunol Rev 243:109–118
55. Choubey D (2012) DNA-responsive inflammasomes and their regulators in autoimmunity. Clin Immunol 142:223–231
56. Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, Roose-Girma M, Erickson S, Dixit VM (2004) Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. Nature 430:213–218
57. Geddes BJ, Wang L, Huang WJ, Lavellee M, Manji GA, Brown M, Jurman M, Cao J, Morgenstern J, Merriam S, Glucksmann MA, DiStefano PS, Bertin J (2001) Human CARD12 is a novel CED4/Apaf-1 family member that induces apoptosis. Biochem Biophys Res Commun 284:77–82
58. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, Fernandes-Alnemri T, Wu J, Monks BG, Fitzgerald KA, Hornung V, Latz E (2009) Cutting edge: NF-κB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol 183:787–791
59. de Koning HD, Bergboer JG, van den Bogaard EH, van Vlijmen-Willems IM, Rodijk-Olthuis D, Simon A, Zeeuwen PL, Schalkwijk J (2012) Strong induction of AIM2 expression in human epidermis in acute and chronic inflammatory skin conditions. Exp Dermatol 21:961–964

60. Hakimi M, Peters A, Becker A, Böckler D, Dihlmann S (2013) Inflammation-related induction of absent in melanoma 2 (AIM2) in vascular cells and atherosclerotic lesions suggests a role in vascular pathogenesis. J Vasc Surg. doi:10.1016/j.jvs.2013.03.048
61. Lamkanfi M, Dixit VM (2012) Inflammasomes and their roles in health and disease. Annu Rev Cell Dev Biol 28:137–161
62. Wen H, Gris D, Lei Y, Jha S, Zhang L, Huang MT, Brickey WJ, Ting JP (2011) Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol 12:408–415
63. De Nardo D, Latz E (2011) NLRP3 inflammasomes link inflammation and metabolic disease. Trends Immunol 32:373–379
64. Tack CJ, Stienstra R, Joosten LA, Netea MG (2012) Inflammation links excess fat to insulin resistance: the role of the interleukin-1 family. Immunol Rev 249:239–252
65. Salminen A, Ojala J, Kaarniranta K, Kauppinen A (2012) Mitochondrial dysfunction and oxidative stress activate inflammasomes: impact on the aging process and age-related diseases. Cell Mol Life Sci 69:2999–3013
66. Lopez-Castejon G, Pelegrin P (2012) Current status of inflammasome blockers as anti-inflammatory drugs. Expert Opin Investig Drugs 21:995–1007
67. Stehlik C, Dorfleutner A (2007) COPs and POPs: modulators of inflammasome activity. J Immunol 179:7993–7998
68. Rathinam VA, Vanaja SK, Fitzgerald KA (2012) Regulation of inflammasome signaling. Nat Immunol 13:333–342
69. Bergsbaken T, Fink SL, Cookson BT (2009) Pyroptosis: host cell death and inflammation. Nat Rev Microbiol 7:99–109
70. Fernandes-Alnemri T, Wu J, Yu JW, Datta P, Miller B, Jankowski W, Rosenberg S, Zhang J, Alnemri ES (2007) The pyroptosome: a supramolecular assembly of ASC dimers mediating inflammatory cell death via caspase-1 activation. Cell Death Differ 14:1590–1604
71. Cheng J, Waite AL, Tkaczyk ER, Ke K, Richards N, Hunt AJ, Gumucio DL (2010) Kinetic properties of ASC protein aggregation in epithelial cells. J Cell Physiol 222:738–747
72. Miao EA, Rajan JV, Aderem A (2011) Caspase-1-induced pyroptotic cell death. Immunol Rev 243:206–214
73. Aachoui Y, Sagulenko V, Miao EA, Stacey KJ (2013) Inflammasome-mediated pyroptotic and apoptotic cell death, and defense against infection. Curr Opin Microbiol 16:319–326
74. Broz P, von Moltke J, Jones JW, Vance RE, Monack DM (2010) Differential requirement for Caspase-1 autoproteolysis in pathogen-induced cell death and cytokine processing. Cell Host Microbe 8:471–483
75. Pierini R, Juruj C, Perret M, Jones CL, Mangeot P, Weiss DS, Henry T (2012) AIM2/ASC triggers caspase-8-dependent apoptosis in *Francisella*-infected caspase-1-deficient macrophages. Cell Death Differ 19:1709–1721
76. Sagulenko V, Thygesen SJ, Sester DP, Idris A, Cridland JA, Vajjhala PR, Roberts TL, Schroder K, Vince JE, Hill JM, Silke J, Stacey KJ (2013) AIM2 and NLRP3 inflammasomes activate both apoptotic and pyroptotic death pathways via ASC. Cell Death Differ 20:1149–1160
77. Ippagunta SK, Malireddi RK, Shaw PJ, Neale GA, Walle LV, Green DR, Fukui Y, Lamkanfi M, Kanneganti TD (2011) The inflammasome adaptor ASC regulates the function of adaptive immune cells by controlling Dock2-mediated Rac activation and actin polymerization. Nat Immunol 12:1010–1016
78. Ippagunta SK, Malireddi RK, Shaw PJ, Neale GA, Walle LV, Fukui Y, Green DR, Lamkanfi M, Kanneganti TD (2012) Addendum: defective Dock2 expression in a subset of ASC-deficient mouse lines. Nat Immunol 13:701–702
79. Ohtsuka T, Liu XF, Koga Y, Kitajima Y, Nakafusa Y, Ha CW, Lee SW, Miyazaki K (2006) Methylation-induced silencing of ASC and the effect of expressed ASC on p53-mediated chemosensitivity in colorectal cancer. Oncogene 25:1807–1811
80. Siraj AK, Hussain AR, Al-Rasheed M, Ahmed M, Bavi P, Alsobhi SA, Al-Nuaim A, Uddin S, Al-Kuraya K (2011) Demethylation of TMS1 gene sensitizes thyroid cancer cells to TRAIL-induced apoptosis. J Clin Endocrinol Metab 96:E215–E224
81. Nakajima K, Takeoka M, Mori M, Hashimoto S, Sakurai A, Nose H, Higuchi K, Itano N, Shiohara M, Oh T, Taniguchi S (2010) Exercise effects on methylation of ASC gene. Int J Sports Med 31:671–675
82. Gentilini D, Mari D, Castaldi D, Remondini D, Ogliari G, Ostan R, Bucci L, Sirchia SM, Tabano S, Cavagnini F, Monti D, Franceschi C, Di Blasio AM, Vitale G (2013) Role of epigenetics in human aging and longevity: genome-wide DNA methylation profile in centenarians and centenarians' offspring. Age (Dordr) 35:1961–1973
83. Youm YH, Kanneganti TD, Vandanmagsar B, Zhu X, Ravussin A, Adijiang A, Owen JS, Thomas MJ, Francis J, Parks JS, Dixit VD (2012) The Nlrp3 inflammasome promotes age-related thymic demise and immunosenescence. Cell Rep 1:56–68
84. Yeretssian G, Labbe K, Saleh M (2008) Molecular regulation of inflammation and cell death. Cytokine 43:380–390
85. Ashida H, Mimuro H, Ogawa M, Kobayashi T, Sanada T, Kim M, Sasakawa C (2011) Cell death and infection: a double-edged sword for host and pathogen survival. J Cell Biol 195:931–942
86. Liu HD, Li W, Chen ZR, Hu YC, Zhang DD, Shen W, Zhou ML, Zhu L, Hang CH (2013) Expression of the NLRP3 inflammasome in cerebral cortex after traumatic brain injury in a rat model. Neurochem Res 38:2072–2083
87. Li Y, Xu S, Jiang B, Cohen RA, Zang M (2013) Activation of sterol regulatory element binding protein and NLRP3 inflammasome in atherosclerotic lesion development in diabetic pigs. PLoS ONE 8:e67532
88. Segovia J, Sabbah A, Mgbemena V, Tsai SY, Chang TH, Berton MT, Morris IR, Allen IC, Ting JP, Bose S (2012) TLR2/MyD88/NF-κB pathway, reactive oxygen species, potassium efflux activates NLRP3/ASC inflammasome during respiratory syncytial virus infection. PLoS ONE 7:e29695
89. Ding Y, Li J, Liu S, Zhang L, Xiao H, Li J, Chen H, Petersen RB, Huang K, Zheng L (2013) DNA hypomethylation of inflammation-associated genes in adipose tissue of female mice after multigenerational high fat diet feeding. Int J Obes (Lond). doi:10.1038/ijo.2013.98
90. Kummer JA, Broekhuizen R, Everett H, Agostini L, Kuijk L, Martinon F, van Bruggen R, Tschopp J (2007) Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response. J Histochem Cytochem 55:443–452
91. Heilbronn LK, Campbell LV (2008) Adipose tissue macrophages, low-grade inflammation and insulin resistance in human obesity. Curr Pharm Des 14:1225–1230
92. Stienstra R, van Diepen JA, Tack CJ, Zaki MH, van de Veerdonk FL, Perera D, Neale GA, Hooiveld GJ, Hijmans A, Vroegrijk I, van den Berg S, Romijn J, Rensen PC, Joosten LA, Netea MG, Kanneganti TD (2011) Inflammasome is a central player in the induction of obesity and insulin resistance. Proc Natl Acad Sci USA 108:15324–15329
93. Cedar H, Bergman Y (2012) Programming of DNA methylation patterns. Annu Rev Biochem 81:97–117
94. Johnson AA, Akman K, Calimport SR, Wuttke D, Stolzing A, de Magalhaes JP (2012) The role of DNA methylation in aging, rejuvenation, and age-related disease. Rejuvenation Res 15:483–494
95. Johansson A, Enroth S, Gyllensten U (2013) Continuous aging of the human DNA methylome throughout the human lifespan. PLoS ONE 8:e67378

96. Lu H, Ouyang W, Huang C (2006) Inflammation, a key event in cancer development. Mol Cancer Res 4:221–233
97. Zitvogel L, Kepp O, Galluzzi L, Kroemer G (2012) Inflammasomes in carcinogenesis and anticancer immune responses. Nat Immunol 13:343–351
98. Kolb R, Liu GH, Janowski AM, Sutterwala FS, Zhang W (2013) Inflammasomes in cancer: a double-edged sword. Protein Cell. doi:10.1007/s13238-013-3051-8
99. Allen IC, TeKippe EM, Woodford RM, Uronis JM, Holl EK, Rogers AB, Herfarth HH, Jobin C, Ting JP (2010) The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. J Exp Med 207:1045–1056
100. Zaki MH, Lamkanfi M, Kanneganti TD (2011) The Nlrp3 inflammasome: contributions to intestinal homeostasis. Trends Immunol 32:171–179
101. Zaki MH, Vogel P, Body-Malapel M, Lamkanfi M, Kanneganti TD (2010) IL-18 production downstream of the Nlrp3 inflammasome confers protection against colorectal tumor formation. J Immunol 185:4912–4920
102. Qin JZ, Chaturvedi V, Denning MF, Choubey D, Diaz MO, Nickoloff BJ (1999) Role of NF-κB in the apoptotic-resistant phenotype of keratinocytes. J Biol Chem 274:37957–37964
103. Shao W, Yeretssian G, Doiron K, Hussain SN, Saleh M (2007) The caspase-1 digestome identifies the glycolysis pathway as a target during infection and septic shock. J Biol Chem 282:36321–36329