Mini Review Article

The Duality of AIM2 Inflammasome: A Focus on its Role in Autoimmunity and Skin Diseases

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Abstract: Understanding the inflammasome biology is one of the most exciting challenges in immuno-pharmacology. The role of the inflammasomes has been recognized in the host defense mechanism against invading pathogens and in the development of several conditions, such as cancer, auto-inflammatory, autoimmune, metabolic and neurodegenerative disorders. DNA recognition by the cells is a crucial immunological step leading to the initiation of an innate immune response. Absent in Melanoma 2 (AIM2) is a cytoplasmic sensor that perceives double-stranded DNA of microbial or host origin. Once the DNA is bound, AIM2 assembles a multiprotein complex named inflammasome, which drives pyroptosis and proteolytic cleavage of pro-IL-1β and pro-IL-18 pro-inflammatory cytokines, leading to a protective inflammasome-mediated host response. However, improper recognition of self-DNA by AIM2 triggers deleterious inflammatory responses, leading to systemic inflammation and several pathological conditions. Therefore, understanding the mechanisms of AIM2-inflammasome-mediated inflammation will provide an essential knowledge base to develop new successful therapeutic strategies to cure the outlined pathologies in which AIM2- inflammasome activation plays a key role, as well as to guide clinical practice. This mini-review provides an overview on the latest research findings on AIM2 inflammasome, with particular focus on its role in autoimmunity and skin disorders. An update on its therapeutic implications has also been documented.

Keywords: Absent in Melanoma 2 (AIM2), Inflammasome, Autoimmune Disorders, Psoriasis, Inflammation

Introduction

The inflammasomes are innate immune system sensors that control the activation of caspase-1 and promote inflammation towards pathogens and molecules derived from host proteins (Guo *et al*., 2015). They have been associated to a variety of auto-inflammatory and auto-immune diseases, as well as neurodegenerative and metabolic disorders (Strowig *et al*., 2012). In the initiation of the inflammatory process, inflammasomes play key roles in causing, contributing or amplifying the pathology in response to the host-derived factors (Guo *et al*., 2015).

After sensing certain stimuli the appropriate NOD-Like Receptor (NLR) or the non-NLR Absent in Melanoma 2 (AIM2) can oligomerize to be a caspase-1 activating scaffold. The active caspase-1 consequently cleaves the pro-inflammatory IL-1 family of cytokines into their bio-active forms (IL-1β and IL-18), causing pyroptosis, defined as a type of inflammatory cell death (Lamkanfi and Dixit, 2012; Strowig *et al*., 2012). The activation of the inflammasome is therefore a pivotal process mediated by the innate immune system. Recent findings have improved the understanding of this mechanism (Guo *et al*., 2015).

Over the past 10 years, at least 22 NLRs in humans and 34 members in mice have been discovered and widely described (Ting *et al*., 2008). A functional sub-group of NLRs has been identified as driving the formation of the inflammasome (Guo *et al*., 2015). The majority of the inflammasomes characterized so far, show an NLR protein, such as NLRP1, NLRP2, NLRP3, NLRP6, NLRP7, NLRP12, or NLRC4 (NLR-and caspase-activating recruitment domain-containing 4) (de Rivero Vaccari *et al*., 2014). In addition to the NLR

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inflammasomes, the non-NLR-AIM2, has been recognized as a member of the AIM2-Like Receptors (ALRs), consisting of a pyrin and Hin domains, which are essential for inflammasome activation induced by double-stranded DNA (dsDNA) (Liu *et al*., 2015).

The assemblage of an inflammasome complex compels cytosolic sensing of pathogen-associated molecular patterns by a nucleotide-binding domain and leucine-rich repeat receptor (NLR) or Absent in Melanoma 2 (AIM2)-Like Receptors (ALR) (Man and Kanneganti, 2015). To catalyze the proteolytic cleavage of pro-interleukin (IL)-1β and pro-IL-18, which results into pyroptosis, NLRs and ALRs engage caspase-1, through the adapter protein apoptosis-associated speck-like protein, containing a CARD (ASC), (Man and Kanneganti, 2015). To become activated AIM2 or NLRP3 require the polymerization of the N terminal pyridine domain (PYD) of ASC (Lu *et al*., 2014; Cai *et al*., 2014), which, as final step, leads to the formation of a single and distinct inflammasome speck that could be detected in primary macrophages and dendritic cells (DCs) (Man *et al*., 2014; 2015a; Belhocine and Monack, 2012). Recently Bakele and colleagues showed that human neutrophils also express the key components of the NLRP3 and AIM2 inflammasome machinery in different intra-cellular compartments and they are capable to release key cytokines. This findings add valuable knowledge to the well known cytoplasmic localization, described for a variety of cell types (Schroder and Tschopp, 2010), indicating that neutrophils are able to regulate their inflammasomes between intracellular stores, as secretory vesicles and the surface localization. Whether the neutrophils release the vesicles, stored in the inflammasome compartments, into the extracellular microenvironments needs to be further elucidated (Bakele *et al*., 2014). Adamczak *et al*. (2014) reported the presence of a functional AIM2-inflammasome in cortical neurons, which senses aberrant dsDNA through a mechanism leading to neural pyropotosis.

However, inflammasome activation occurs when the scaffold protein senses or binds its activating stimuli. This mechanism is now being clarified for certain inflammasome proteins (Vanaja *et al*., 2015): prominent among these are the roles of NLRC4, NAIP, ASC and AIM2 (Guo *et al*., 2015). The identification of AIM2, as the sensor that triggers inflammasome activation, pyroptosis and release of key cytokines in response to intracellularly delivered dsDNA, has happened in 2009 (Hornung *et al*., 2009; Fernandes-Alnemri *et al*., 2009; Burckstummer *et al*., 2009; Roberts *et al*., 2009). AIM2 recognizes dsDNA in a sequence-independent manner. However, the DNA sequence should be at least 80 base pairs in length (Jin *et al*., 2013). The clarification of the crystal structure of AIM2 had an impact on the explanation of its activation mechanism (Man *et al*., 2016).

This mini-review summarizes the latest research findings on the AIM2 inflammasome, focusing on its role in autoimmunity and skin diseases and discussing its therapeutic implications.

The Duality of AIM2: An Overview

Inflammation is a protective immune-response started by the innate immune system in response to harmful stimuli, such as microbes, dead cells, irritants and it is firmly regulated by the host. A lack of inflammation can lead to infections, while excessive inflammation can cause chronic or systemic inflammatory diseases (Guo *et al*., 2015). Innate immune detection and subsequent immune response depends on the initial recognition of pathogen specific molecular motifs (Smith and Jefferies, 2014). Unknown nucleic acids are key molecules recognized by the immune system, recognition of which occurs mainly through specific receptors, including members of Toll-like receptors, AIM2-like receptors, RIG-I-like receptors and intracellular DNA receptors (Smith and Jefferies, 2014). However, a wide range of pathogens is sensed by AIM2 in mammalian cells.

As shown in Fig. 1, recognition of dsDNA from pathogens by AIM2 heads to protective inflammasome-mediated host responses. In contrast, improper recognition of cytoplasmic self-DNA by AIM2 leads to the development of several pathologies, such as psoriasis, dermatitis, arthritis and other autoimmune and inflammatory diseases (Man *et al*., 2016).

In the first case, during infection of a host cell, microbial DNA and other pathogen-associated molecular patterns are released into the cytoplasm, where they are recognized by cytoplasmic DNA sensors, such as AIM2. AIM2 has been shown to provide immune-surveillance to several pathogenic bacteria like *Listeria monocytogenes*, *Streptococcus pneumonia*, *Staphilococcus aureus* and many others (Rathinam *et al*., 2010; Fernandes-Alnemri *et al*., 2010; Kim *et al*., 2010; Warren *et al*., 2010; Hanamsagar *et al*., 2014; Tsuchiya *et al*., 2010; Man *et al*., 2016). These pathogens activate AIM2 via a 'non canonical' pathway owing to its requirement for type I IFN, analogous to the non-canonical NLRP3 inflammasome pathway (Man *et al*., 2016) and they must escape the vacuole and undergo bacteriolysis in order to induce the activation of the AIM2 inflammasome (Fang *et al*., 2011; Kim *et al*., 2010; Tsuchiya *et al*., 2010). Some bacteria have evolved virulence determinants to prevent release of DNA to avoid cytoplasmic and clearance by inflammasomes (Crane *et al*., 2014; Dotson *et al*., 2013), however there is limited evidence to support the existence of mechanisms used by bacteria to evade or inhibit activation of AIM2, which is overall an extraordinary antimicrobial machinery (Man *et al*., 2016).
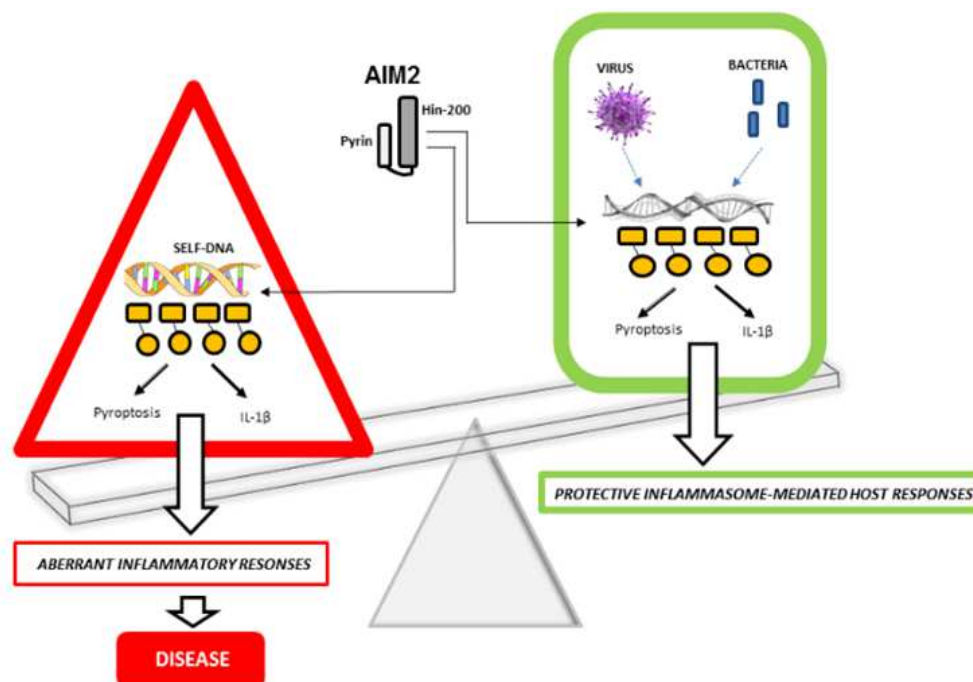
Figure 1. The yin and yang of AIM2 inflammasome. Simplified representation of AIM2 inflammasome activation induced by cytoplasmic dsDNA. AIM2 is formed by a N-terminal pyrin domain and a C-terminal HIN-200 domain, which together form an intramolecular complex that is maintained in an auto-inhibitory state. Upon binding to DNA, AIM2 assembles a multiprotein complex named inflammasome, which catalyzes proteolytic cleavage of pro-IL-1 family cytokines and drives pyropoptosis. Recognition of dsDNA from microbes by AIM2 leads to protective inflammasome-mediated host responses, whereas inappropriate recognition of self-DNA by AIM2 triggers aberrant inflammatory responses, leading to autoimmune diseases, psoriasis, dermatitis, chronic inflammatory diseases, neuroinflammation and metabolic disorders. Therefore, a deep understanding of the balance between the beneficial and the detrimental effects of the inflammasome activation is essential.

Inflammasome responses play also an important role in the host protection against viruses (Kanneganti, 2010; Lupfer *et al*., 2015). Murine cytomegalovirus infections (MCMV) lead to a 'canonical' activation of the AIM2 inflammasome, which doesn't require the type I IFN pathway (Rathinam *et al*., 2010). Recently, Zhen and colleagues showed a reduced expression of IL-1β and IL-18 and caspase-1 through siRNA-mediated silencing of the gene encoding AIM2 in the human glomerular mesangial cell line infected with hepatitis B virus (Zhen *et al*., 2014). Whether, AIM2 recognizes directly viral DNA derived from hepatitis B virus is still elusive: probably the viral DNA binds to AIM2 to trigger inflammasome activation, but the precise molecular mechanisms is not clear (Man *et al*., 2014).

Therefore, to date there is evidence in the literature to indicate that only MCMV, vaccinia viruses and human papilloma viruses induce inflammasome responses in a AIM2-dependent manner (Hornung *et al*., 2009; Rathinam *et al*., 2010; Reinholz *et al*., 2013) and it is known that AIM2 does not respond to all DNA viruses (Man *et al*., 2016). However, has been reported a role for AIM2 in driving IL-1β secretion in response to RNA viruses: silencing of genes encoding AIM2 and caspase-1 reduces proteolytic cleavage and release of

IL-1β in human dermal fibroblasts infected with the RNA virus Chikungunya (Ekchariyawat *et al*., 2015). The mechanism by which AIM2 might sense RNA viruses is still unclear.

Additional to bacteria and viruses AIM2 mediates pathogen recognition of and host defense to the fungal pathogen *Aspergillus fumigatus* and the *Plasmodium berghei ANKA* (Karki *et al*., 2015; Kalantari *et al*., 2014). It has been shown, that mice lacking both AIM2 and NLRP3, ASC or caspase-1 and infected with *A. fumigatus* are more susceptible than infected WT (Karki *et al*., 2015). The requirement for dual sensing of pathogens by both AIM2 and NLRP3 has also been observed in mouse bone marrow-derived macrophages stimulated with *Plasmodium berghei ANKA* infected red-blood cells (Kalantari *et al*., 2014). There is evidence that *A. fumigatus* genomic DNA, transfected into the cell cytoplasm as well as for the *Plasmodium falciparum* genomic DNA, transported into the cytoplasm by hemozoin are recognized by AIM2 directly (Kalantari *et al*., 2014; Karki *et al*., 2015). Further studies to elucidate the mechanisms involved are warranted.

AIM2 also contributes to the control of excessive inflammation in a complex, context-dependent way (Zitvogel *et al*., 2012). For example, it has been shown

that AIM2 is implicated in inflammation and cell death of the brain. Cerebrospinal Fluid (CSF) of patients with traumatic brain injury often contains cell-free DNA fragments rather than the CSF from non-trauma patients and this correlates with mortality (Adamczak et al., 2014; Campello Yurgel et al., 2007). Adamczak and colleagues have demonstrated that human embryonal cortical neurons express functional AIM2 inflammasome, they release IL-1β and they undergo pyroptosis upon AIM2 activation with poly (dA:dT) transfection. Therefore, when exposed to the CSF of traumatic brain injury patients, they showed AIM2 up-regulation and caspase-1 activation compared with embryonic cortical neurons that had been exposed to the CSF of non-trauma patients, indicating that CSF from injured patients is immunogenic and may cause pyropotosis in neighboring cells (Adamczak et al., 2014). These findings establish neuronal pyroptosis as a neuronal cell death mechanism, induced by activation of the AIM2 inflammasome (Adamczak et al., 2014). In the context of cancer, beyond its role in killing infected macrophages, pyroptosis may participate to the cell-autonomous tumor suppression. This suggests that the inflammasomes can positively influence the cell-autonomous death pathways and anticancer immune-surveillance, but they can also induce autocrine or paracrine processes that favor carcinogenic inflammation, tumor growth, metastasis and angiogenesis (Zitvogel et al., 2012; Miao et al., 2011). In support of the role of AIM2 inflammasome as a suppressor of cancer, it has been found that colorectal cancer patients, whose tissues showed a reduced AIM2 expression have a poorer prognosis compared to those with an up-regulation of AIM2 (Dihlmann et al., 2014). Moreover, AIM2 down-regulation has also been reported in prostate cancer (Ponomareva et al., 2013), whereas increased expression has been detected in nasopharyngeal carcinoma (Wang et al., 2012; Chen et al., 2012), oral squamous cell carcinoma (Kondo et al., 2012) and lung adenocarcinoma (Kong et al., 2015), suggesting that the differential expression of AIM2 in a range of tumor tissues could relate to its possible unique role in different types of cancer (Man et al., 2016). The mechanism by which AIM2 regulates tumorigenesis has been demonstrated by Wilson et al. (2015) and described in a mouse model of colitis-associated colorectal cancer (Man et al., 2015b). The above-mentioned studies have demonstrated that AIM2 works independently of the inflammasome to prevent colorectal cancer. Although differential secretion of the key cytokines, including TNFα and IL-6, was not observed among WT and Aim2$^{-/-}$ mice, proliferation of enterocytes was more pronounced in Aim2$^{-/-}$ mice (Man et al., 2015b; Wilson et al., 2015). Wilson and colleagues discovered a DNA-PK, a kinase that can phosphorylate and activate AKT, as a binding partner of AIM2, through which, AIM2 suppresses DNA-PK activation (Wilson et al., 2015; Feng et al., 2004; Lu et al., 2006). Very recently, Man and colleagues also showed that a reciprocal exchange of the microbiota between Aim2$^{-/-}$ and WT mice could cause a decrease in tumorigenesis in Aim2$^{-/-}$ and an increase in tumorigenesis in WT mice (Man et al., 2015b). Collectively these studies provide insights into the function of AIM2 as tumor suppressor, especially in colorectal cancer. However, as discussed above, AIM2 inflammasome dysregulation, in terms of incorrect recognition of cytoplasmic self-DNA is reported to result in auto-inflammatory and auto-immune diseases (Smith and Jefferies, 2014; Choubey and Panchanathan, 2008).

AIM2 in Autoimmunity and Skin Diseases

The presence of altered self-DNA may be sensed in the nuclear compartment of cells, leading to inflammation and auto-immune responses (Choubey and Panchanathan, 2008; Fish, 2008). Systemic autoimmune diseases include Sjogren's Syndrome (SS), Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and Systemic Sclerosis (SSc) (Choubey and Panchanathan, 2008). These disorders are characterized by self-antigen-driven immune responses that target host tissues and organs for damage (Crispin et al., 2010). Patients with systemic auto-immune diseases exhibit the so called "IFN-signature", since they show elevated serum levels of pro-inflammatory cytokines, such as IL-1, TNFα, IFNs (Apostolidis et al., 2011; van der Pouw Kraan et al., 2007). It has been demonstrated, that mature SLE neutrophils, which are primed by increased levels of type I IFN, die when they are exposed to SLE-derived anti-ribonucleoprotein antibodies. Death of neutrophils leads to the release of neutrophil extracellular traps, containing genomic DNA (Garcia-Romo et al., 2011; Lande et al., 2011). It has been recently shown by Bakele and colleagues that human neutrophils express the machinery of NOD-like receptor family and AIM2 inflammasome (Bakele et al., 2014). Therefore, upon sensing self-derived DNA, the DNA receptors begin the immune responses (Choubey and Panchanathan, 2008). Several studies also indicate that lupus-associated pathogenesis includes an impaired clearance of dead cellular debris followed by an aberrant activation of the immune system (Baccala et al., 2009; Munoz et al., 2010). As a consequence, it has been proposed that activation of the innate immune responses, which are initiated by DNA sensors, such as AIM2, in cells contributes to the inflammatory responses in Systemic Lupus Erythematosus (SLE) (Munoz et al., 2010). In SLE, self-DNA is often complexed with nuclear antigens and the corresponding auto-antibodies (Marshak-Rothstein, 2006). Thus, the recognition of self-DNA by immune cells has a critical role in a feed forward loop, which promotes auto-antibody production, triggers

innate immune responses and associated immunopathology in SLE and possibly other autoimmune disorders (Choubey and Panchanathan, 2008; Munoz *et al*., 2010; Baccala *et al*., 2007). Interestingly, a recent study by Kahlenberg and colleagues has demonstrated that expression of AIM2 gene is induced by IFN-α in Endothelial Progenitor Cells (EPCs) and Circulating Angiogenic Cells (CACs) (Kahlenberg *et al*., 2011). Considering the increase of premature atherosclerosis, associated with endothelial dysfunction, up to 50-fold, in SLE patients (Kahlenberg *et al*., 2011), it has been proposed that an imbalance between endothelial cell damage and repair, triggered by the enhanced inflammasome activity, may lead to a faster atherosclerosis through increased IL-18 activation (Kahlenberg *et al*., 2011; Kaplan, 2011). In addition, several studies demonstrated that the expression of the gene encoding AIM2 is increased in immune cells of male patients with SLE and both increases and decreases in AIM2 expression have been observed in female patients (Yang *et al*., 2015; Kimkong *et al*., 2009). Further, DNA methylation of the gene encoding AIM2 is decreased in patients with SLE compared with their healthy siblings, suggesting that epigenetic changes could also contribute to the development of this disease (Javierre *et al*., 2010).

The inability to degrade self-DNA also play a role in the pathogenesis of autoimmune polyarthritis (Man *et al*., 2016). It has been shown by Kawane and colleagues that mice lacking the lysosomal endonuclease DNAse II (*Dnase II*$^{-/-}$ mice) are embryonically lethal, due to the impaired ability to degrade self-DNA by macrophages (Kawane *et al*., 2001). Genomic deletion of type I IFN Receptor (IFNAR) rescued *Dnase* II$^{-/-}$ mice from embryonic lethality (Yoshida *et al*., 2005), but the mice lacking both IFNAR and DNAse II (*Dnase II*$^{-/-}$*Ifnar*$^{-/-}$ mice) would develop polyarthritis (Kawane *et al*., 2001). Interestingly, Baum and colleagues demonstrated a peculiar role for the AIM2 inflammasome in arthritis pathogenesis. The group showed that genomic deletion of AIM2 and STING halted inflammasome activation, macrophage infiltration in the joint and consequently the development of arthritis in Dnase II$^{-/-}$Ifnar$^{-/-}$mice (Baum *et al*., 2015; Jakobs *et al*., 2015). This suggests that multiple DNA sensors might contribute to the inappropriate DNA recognition leading to the pathogenesis of a clinical disease (Man *et al*., 2016).

Accumulated DNA could result into an endogenous danger signal and it has been shown to trigger AIM2-dependent release of IL-1β from keratinocytes, contributing to the pathogenesis of psoriasis (Dombrowski *et al*., 2011). Dombrowski and colleagues demonstrated the presence of cytosolic DNA and subsequent up-regulation of AIM2 in keratinocytes of psoriatic lesions versus healthy controls. Furthermore, they showed that cathelicidin LL-37, upon internalization into the cytosol of keratinocytes, was able to neutralize the cytosolic DNA and its pro-inflammatory effect, interfering with AIM2 activation and therefore acting as a physiologic inhibitor of AIM2 inflammasome (Dombrowski *et al*., 2011; 2012). In addition, de Koning *et al*. (2012) observed a strong epidermal up-regulation of AIM2 protein expression in psoriasis, atopic dermatitis (AD), venous ulcera, contact dermatitis and experimental wounds, highlighting the dynamics of epidermal AIM2 expression and showing an important induction of Langherans cells and melanocyte-restricted expression in sub-populations of epidermal keratinocytes under inflammatory conditions, compared to normal epidermis. The remarkable increase of AIM2 expression in keratinocytes at site of acute and chronic skin barrier disruption-related inflammation, indicates a role for AIM2 inflammasome in both antimicrobial defense and also sustained chronic inflammation (de Koning *et al*., 2012). However, Kopfnagel and colleagues obtained contrasting results, suggesting that there is no intrinsic abnormality concerning the expression of AIM2 in keratinocytes of AD or psoriatic patients versus healthy controls, pointing out a general role of AIM2 in skin defense (Kopfnagel *et al*., 2011). Further investigations would be necessary to elucidate the contribution of AIM2 in inflammatory skin conditions. However, AIM2 up-regulation upon skin barrier disruption serves as first line of defense against invading pathogens (Fernandes-Alnemri *et al*., 2009; 2010, Hornung *et al*., 2009, Kim *et al*., 2010, Rathinam *et al*., 2010). This could also favor wound healing, however, if the barrier impairment persists, AIM2-induced IL-1β activation could promote an inflammatory loop in chronic skin disorders, such as psoriasis, AD and even venous leg ulcers (de Koning *et al*., 2012).

Therapeutic Implications of AIM2 Inflammasome

Although the therapeutic inhibition of the inflammasomes has to be balanced against its beneficial contribution, it is well known that inflammasome dysregulation leads to the pathogenesis of several diseases, including neurodegenerative and metabolic disorders as well as auto-inflammatory and autoimmune diseases. Thus, the development of new targeted drugs against the inflammasomes would be necessary for the treatment of these pathologies. The majority of available small-molecules inhibitors target NLPR3 inflammasome, but not NLRC4 or AIM2. The therapies that modulate either the NLPR3 inflammasome complex itself and the two cytokines, which is responsible for activating, are broadly detailed and recently reviewed already by Ozaki *et al*. (2015) and Baldwin *et al*. (2015). Here, a focus and an update on the AIM2 inflammasome-targeted molecules is documented and summarized in Table 1.

Table 1. Therapeutic agents targeting AIM2- inflammasome components and their clinical status

Therapeutic agent	Target	Clinical Status/Use
Parthenolide	AIM2 (indirectly)	Not suitable for clinical trials due to
	Caspase-1	its poor bioavailability and solubility
	ASC pyropoptosome formation	
Bay 11-7082	AIM2 (indirectly)	Approved
	ASC pyropoptosome formation	Systemic lupus erythematosus
Cholesterol 25-hydroxylase (Ch25h)	AIM2 (indirectly)	N/A
	IL-1β (regulate Il1b transcription)	
PRT062607 (Biogen, Idec,	AIM2 (indirectly)	
Cambridge MA, USA)	Tyrosine kinases	Under evaluation
	ASC speck formation	
R-788 (AstraZeneca)	AIM2 (indirectly)	Abandoned
	Tyrosine kinases	for low specificity and high toxicity
Pralnacasan (VX-740)	AIM2 (indirectly)	Tested in clinical trials for RA, but outcome
	Caspase-1	of the clinical trial is not reported
Cys-LT-receptor (Bayer AG, Leverkusen,	AIM2 (indirectly)	Approved
Germany/US Patent 7,498,460, 2009)	ASC oligomerization	Allergic rhinitis, asthma, nasal polyposis
ASC monoclonal Ab (clone 23-4,	AIM2 (indirectly)	N/A
MBL, Nagoya, Japan)	ASC inhibition	Experimental research use
Synthetic Oligodeoxynucleotides (ODN)	AIM2	N/A
containing suppressive TTAGGG motifs	ASC dimerization	Experimental research use
	AIM2 inflammasome assembly	
Bromoxone	AIM2 (indirectly)	N/A
	Caspase-1	
	ASC	
Probenecid	AIM2 (indirectly)	Approved
	Neural pyroptosis	(under investigation its use to inhibit neural
		pyroptosis during AIM2 inflammasome stimulation)

Abbreviations: AIM2, Absent in Melanoma 2; ASC, apoptosis-related speck-like protein containing a caspase recruitment domain; Cys-LT-receptor, cystenyl leukotriene, RA, rheumatoid arthritis; IL-1, Interleukin-1; The table summarizes the most recent therapeutic agents targeting the AIM2-inflammasome components described in the literature, therefore it is not exhaustive. Each therapeutic agent listed in the table has been detailed and referenced in the text.

Several small-molecule inhibitors targeting NLRP3, NLRP1, NLRC4 and AIM2 have been characterized and widely described in (Ozaki *et al*., 2015), even if their potency for *in vivo* usage needs further evaluation. The large majority of these are pharmacologic inhibitors that have been repurposed to target the inflammasome (Guo *et al*., 2015) and they include: Parthenolide (Juliana *et al*., 2010), Bay 11-708 (Juliana *et al*., 2010), CRID3 (Coll *et al*., 2011), Auranofin (Isakov *et al*., 2014), Isoliquiritigenin (Honda *et al*., 2014), 3,4-methylenedioxy-β-nitrostyrene (He *et al*., 2014), Cyclopentenone prostaglandin 15d-PJ$_2$ (Maier *et al*., 2015) and 25-Hydroxycholesterol (25-HC) (Reboldi *et al*., 2014). Moreover, type I interferon has been shown to also suppress inflammasome activation with a poorly understood mechanism (Guarda *et al*., 2011). However, recently it has been demonstrated that an IFN-stimulated gene product, cholesterol 25-hydroxylase (Ch25h), antagonizes both Il1b transcription and NLRP3, NLRC4 and AIM2 inflammasome activation, indicating that Ch25h has a broad inhibitory activity of multiple inflammasomes (Reboldi *et al*., 2014).

Interestingly, Hara *et al*. (2013) observed that, upon NLRP3 and AIM2 inflammasome activation, the tyrosine kinases Syk and Jnk regulate ASC speck formation. Phosphorylation of ASC is critical for inflammasomes aggregation, consequent pro-caspase-1 recruitment and cytokines release (Hara *et al*., 2013). These findings supported a growing interest in Syk and Jnk in the inflammatory response. Accordingly, several drugs, targeting these kinases have been recently tested in patients suffering from severe auto-inflammation (Grimminger *et al*., 2010; Laudisi *et al*., 2014). Meanwhile a promising candidate (PRT062607, Biogen Idec, Cambridge, MA, USA) is under evaluation, previous Syk inhibitors, such as AstraZeneca, R-788, showed low specificity and high toxicity, which forced to abandon their development (Genovese *et al*., 2011; Flight, 2012). Regardless, Hara and colleagues have showed that specific inhibition of phosphorylated ASC could represent an alternative means to enable suppression of caspase-1 activation and the associated pathological consequences (Laudisi *et al*., 2014). To this end, Pralnacasan (VX-740, Vertex Pharmaceuticals, Inc.

Cambridge, MA, USA) is a specific caspase-1 inhibitor, which showed promising in animal model of osteoarthritis, but, unfortunately its toxicity was too high for clinical development (Rudolphi *et al.*, 2003). Overall, this approach may enable more selective blocking of IL-1 maturation and release, without the toxicity associated with kinase inhibition (Laudisi *et al.*, 2014). Interestingly, a cysteinyl leukotriene receptor antagonist developed by Bayer Pharmaceuticals (Bayer AG, Leverkusen, Germany/Härter *et al*, US Patent 7.498.460, 2009) (Ozaki *et al.*, 2015; Coll *et al.*, 2011; Haerter *et al.*, 2009) was described and found to inhibit both NLRP3 and AIM2 inflammasome-induced IL-1β processing, by preventing ASC oligomerization and it also appears to have further roles in innate immune responses, different from its role of adaptor for inflammasome formation (Ozaki *et al.*, 2015). Therefore, this small-molecule inhibitor of ASC may hold therapeutic promise as a dual-purpose therapy in some inflammatory conditions (Coll *et al.*, 2011). It has been reported the use of an anti-human ASC monoclonal antibody (clone 23-4, MBL, Nagoya, Japan) for ASC identification, cloning and characterization (Masumoto *et al.*, 2001). Kaneko *et al.* (2015) have studied whether this anti-ASC human antibody would interfere with PYD of ASC and if it could then be considered a therapeutic candidate against disorders due to AIM2-inflammasome dysregulation. Since AIM2 is an intracellular receptor, enforced internalization of both ligands and candidate molecules is necessary for pharmacological screening. Interestingly, the authors developed a reconstituted *in vitro* AIM2 inflammasome in a cell-free system, which may serve as a useful tool to screen AIM2 inflammasome-targeting therapeutics (Kaneko *et al.*, 2015).

Inhibiting AIM2 inflammasome activity using synthetic inhibitors, such as synthetic Oligodeoxynucleotides (ODN) containing suppressive TTAGGG Motifs (Kaminski *et al.*, 2013) or taking advantage of endogenous AIM2 inhibitors, such as the pyrin-containing proteins, recently described by (Khare *et al.*, 2014; de Almeida *et al.*, 2015), or antimicrobial cathelicidin peptides, reported by Schauber and colleagues (Dombrowski *et al.*, 2011), could certainly be explored and studied for their potential to limit undesired inflammation (Man *et al.*, 2016). Still, further research aiming at the discovery of new small-molecules to inhibit AIM2 inflammasome would certainly be of benefit to the development of effective drugs to treat chronic diseases, in which inflammation is the key player.

Conclusion and Perspective

Understanding the inflammasome activity is crucial for host response to microbes and possibly for ideal response to vaccine adjuvants (Guo *et al.*, 2015). Given that, not all inflammasome activation can be considered harmful, it is very important to have a greater knowledge of the balance between beneficial and deleterious effects caused by inflammasome activation. For example, in the context of cancer, inflammasomes play pleiotropic roles since they could positively influence anti-cancer immuno-surveillance, but they can also induce carcinogenic inflammation, tumor growth, metastasis and angiogenesis. Due to such ambiguity, it is not possible to express definite advices to either inhibit or stimulate the inflammasomes or their products in cancer therapy: depending on the type of neoplasm, inflammasome inhibition maybe recommended as a therapeutic option or counter indicated (Guo *et al.*, 2015). With regard to neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis, recently, it has been shown that the inflammasome modulates neuroinflammatory cells and the initial stages of neuro-inflammation. The activation of the inflammasome, upon a subsequent cascade of events, correlated to neuro-inflammation (such as oxidative stress), makes it, indeed, a promising therapeutic target for the modulation of these disorders (Freeman and Ting, 2016).

However, over-activation of the sensing mechanisms for RNA and DNA recognition or the incapability to properly control and restrain the responses is directly linked to auto-immune disorders (Smith and Jefferies, 2014). As widely discussed herein, focusing on AIM2 inflammasome, it is known that aberrant recognition of cytoplasmic self-DNA by AIM2 leads to the development of several pathologies, like psoriasis, dermatitis, arthritis and other autoimmune and chronic inflammatory diseases. Therefore, here the need and the challenge of understanding and dissecting deeper the molecular mechanisms through which innate immune cells sense self-DNA and initiate an immune-response. This will enable to identify new therapeutic agents to effectively target AIM2 activated by dsDNA and consequently treat the related autoimmune/inflammatory diseases and conditions. In addition, further characterization of the neuronal AIM2 inflammasome and pyroptosis could also serve as an effective tool for the progression and the development of new therapies to control and restrain both the inappropriate autoimmune reactions to host nucleic acids and the pathologic sequelae of neuro-inflammation.

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Disclosure Statement

The author declare no conflict of interest

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