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Review

Aspirin and immune system

Muzammal Hussain [a,1], Aqeel Javeed [a,*,1], Muhammad Ashraf [a], Yong Zhao [b], Muhammad Mahmood Mukhtar [c], Muti Ur Rehman [d]

[a] Department of Pharmacology & Toxicology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[b] Transplantation Biology Research Division, State Key Laboratory of Biomembrane and Membrane Biotechnology, Institute of Zoology, Chinese Academy of Sciences, Datun Road, Beijing 100101, China
[c] Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
[d] Department of Pathology, University of Veterinary and Animal Sciences, Lahore, Pakistan

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ABSTRACT

The time-tested gradual exploration of aspirin's diverse pharmacological properties has made it the most reliable therapeutic agent worldwide. In addition to its well-argued anti-inflammatory effects, many new and exciting data have emerged regarding the role of aspirin in cells of the immune system and certain immunopathological states. For instance, aspirin induces tolerogenic activity in dendritic cells and determines the fate of naive T cells to regulatory phenotypes, which suggests its immunoregulatory potential in relevance to immune tolerance. It also displays some intriguing traits to modulate the innate and adaptive immune responses. In this article, the immunomodulatory relation of aspirin to different immune cells, such as neutrophils, macrophages, dendritic cells (DCs), natural killer (NK) cells, and the T and B lymphocytes has been highlighted. Moreover, the clinical prospects of aspirin in terms of autoimmunity, allograft rejection and immune tolerance have also been outlined.

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1. Introduction

Acetylsalicylic acid (ASA) or aspirin represents the prototype of non-steroidal anti-inflammatory drugs. Initially, after its innovative follow up from salicylic acid by Felix Hoffman (1897), ASA had been

* Corresponding author at: Department of Pharmacology & Toxicology, University of Veterinary and Animal Sciences, Abdul Qadir Jilani Road, Lahore, 54600, Pakistan. Tel.: +92 42 9211449; fax: +92 429211461.
E-mail address: aqeel.javeed@uvas.edu.pk (A. Javeed).
[1] These authors equally contributed to this work.

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reported as the world's first truly synthetic drug possessing anti-inflammatory activity against rheumatism. At present, ASA has achieved clinical prominence as a globally relied therapeutic agent not only because of its traditional anti-inflammatory paradigm, but also for its more advanced life-saving perspective related to cardiovascular events (heart attacks, stroke, etc.) [1]. Moreover, the nitric oxide (NO) derivatives of ASA (the NO-aspirins such as NCX-4016, NCX-4040, etc.) are also acquiring clinical approval because of their gastroprotective peculiarity as compared to ASA [2–4]. Pharmacologically, ASA exerts its anti-inflammatory effects through its typical cyclooxygenase (COX) inhibitory mechanism of action [5,6]. However, it has now been definitely explored that ASA also exerts variety of its anti-inflammatory actions via biosynthesis of proresolution 15R-epilipoxin A4, the so-called aspirin-triggered lipoxins (ATLs) [7,8]. In addition, clearly evident data suggests that ASA also have some COX-independent mechanisms, including induction of NO release [9], enhancement of adenosine production by increasing adenosine triphosphate hydrolysis [10,11], and the inhibition of nuclear factor-kappa B (NF-kB) transcriptional pathway [12].

As an extension of its pharmacological actions, ASA also exhibits the immunopharmacological properties. This is noteworthy that interest in the immunoregulatory ability of ASA has exploded in the last three or four decades and a number of studies have outlined its apparent immunomodulating role. In this review, we will discuss the ASA-mediated immune regulation focusing on its effects on different immune cells, including neutrophils, macrophages, dendritic cells (DCs), natural killer (NK) cells, T effector cells, T regulatory (Treg) cells, and B cells. In addition, we will also highlight the clinical prospective of ASA in terms of autoimmunity, allograft rejection and immunotolerance.

2. Inflammation, prostanoids and the immune system

In general, the principal role of the immune system is to protect the host from the invading pathogenic assailants (microbial or non-microbial). The concept of self-tolerance describes that, despite all of the discretionary aptitude to contend against infectious or non-infectious foreign agents, the immune system does not induce rejection against self-antigens [13,14]. Notwithstanding, the collapse of self-tolerance can trigger an immunologic culprit attack against self-antigens and may lead to a diverse array of autoimmune diseases targeting almost every part of the body [15]. The disruption of the self and non-self discriminatory nature of the immune system may also make it a primary perpetrator in transplant rejection. Generally, it is thought that the underlying immunopathological mechanisms in the sudden offensiveness of the immune system share a common reaction-the immune-mediated chronic inflammation that may involve multiple convergent pathways, such as cytotoxic antibodies, immune complexes, and T cell-mediated delayed-type hypersensitivity reactions.

Inflammation is an integral part of the immune system, which directs and/or shares many cellular and humoral attributes of a typical immune response. In fact, acute phase inflammation is the foremost defensive activity launched by innate immune reactions; however, if not resolved properly, it may deteriorate to the chronic phase and provide a liaison between the humoral and cellular components of adaptive immunity, which may result either in a beneficial termination or a progressively destructive complication that would be harmful to the host [16,17]. Accumulating evidence suggests that chronic inflammation plays a pivotal role in the defensive/offensive dichotomy of the immune system by causing high expression of inflammatory mediators, including COX-mediated production of inflammatory cytokines and the prostanoids (such as prostaglandins (PGs), prostacyclin and thromboxanes) from arachidonic acid, which play an important role in the modulation of immune response. Especially, COX-dependent production of PGs, such as PGD2, PGE2, PGI2, 15-deoxy-Δ12, 14-PGJ2 (15-d-PGJ2), and thromboxane A2, is thought to play a critical role in modulating the immune response mediated by different types of immune cells, thereby playing an important role in the physiology and pathology of immunologic responses in tolerance, autoimmunity, allograft rejection and cancer [18,19]. In short, the prostanoids-mediated immune regulation, particularly of the PGs, appears to be very complex as marked by a set of diverse and often opposing effects within the immune system [20–32], although PGE2-mediated suppression of T helper 1 (Th1) activation and the up-regulation of Th2-type immune responses is the prominent aspect [18,33].

Conceptually, it seems likely that ASA, through its most well-known COX inhibitory mechanism, may prevent the formation of prostanoids and, consequently, modulate the prostanoids-mediated immune regulation; however, it remains largely speculative because of the meager or unestablished experimental/clinical revelations in this regard. Most probably, COX-independent actions of ASA, at higher doses (concentrations), on immunocytes via ATLs, NO, or blockade of NF-kB or other signaling pathways are of arguable relevance. The majority of contributing data in this review, therefore, mainly addresses the relevance of COX-independent mechanisms of ASA to immune regulation, although COX-dependent mechanism will also be discussed where relevant.

3. ASA and immune cells

3.1. ASA and neutrophils

Neutrophils are the key players of innate immunity. After extravasation (adhesion, transmigration, chemotaxis, etc.) from circulatory system toward the site of infection or tissue damage, they produce a variety of inflammatory cytokines and chemokines through the involvement of NF-kB and mitogen-activated protein kinase (MAPK) pathways [34].

ASA can suppress the neutrophil-mediated innate immune responses by decreasing their extravasation, a distinctive step in the innate immunity (Fig. 1). Different lines of evidence suggest that ASA can decrease the adherence of neutrophils to the endothelial lining by its COX-independent mechanisms. It can suppress the inducible expression of genes encoding variety of adhesion molecules (e.g. intracellular adhesion molecule-1 (ICAM-1), P-selectin, CD11b/CD18, etc.) via interference with some transcriptional pathways; inhibits the activation and translocation of NF-kB from cytosol to nucleus [12,35], and blocks the activation of MAPK or extracellular regulated kinase (Erk) signaling the Raf-1/Mek signal transduction pathway [36,37]. ASA can also halt neutrophilic extravasation through ATLs, which can potently inhibit the recruitment cascade of neutrophils during an immune-mediated inflammatory response (Fig. 1) [38,39]. They can interfere with the neutrophil adhesion [40], transmigration [41], and chemotaxis [42] via interaction with their specific lipoxin A4 receptor [43,44]. They inhibit the leukocyte–endothelial interactions by producing antiadhesive NO [45], antagonize the tumor necrosis factor (TNF)α-mediated neutrophil adherence and transmigration across endothelial cells [46], and block the phosphorylation of leukocyte-specific protein-1 (a downstream component of p38-MAPK cascade), which is known to promote chemotaxis in neutrophils [47]. Another study indicated that ASA can also inhibit the transendothelial neutrophilic migration through generation of 17R-epimer-resolvin D1, the so-called aspirin-triggered resolvin D1 [48]. In addition, NCX-4016 (a NO-aspirin) has been described to inhibit the lipopolysaccharide (LPS) — and interleukin (IL) -1β induced cell-to-cell adhesion through the formation of ATLs and NO at the neutrophil/human umbilical vein endothelial cell interface [49]. The gel shift analysis revealed that NCX-4016 suppressed the overexpression of ICAM-1 and E-selectin through inhibition of NF-kB pathway in the human umbilical vein endothelial cell. Collectively, ASA and its

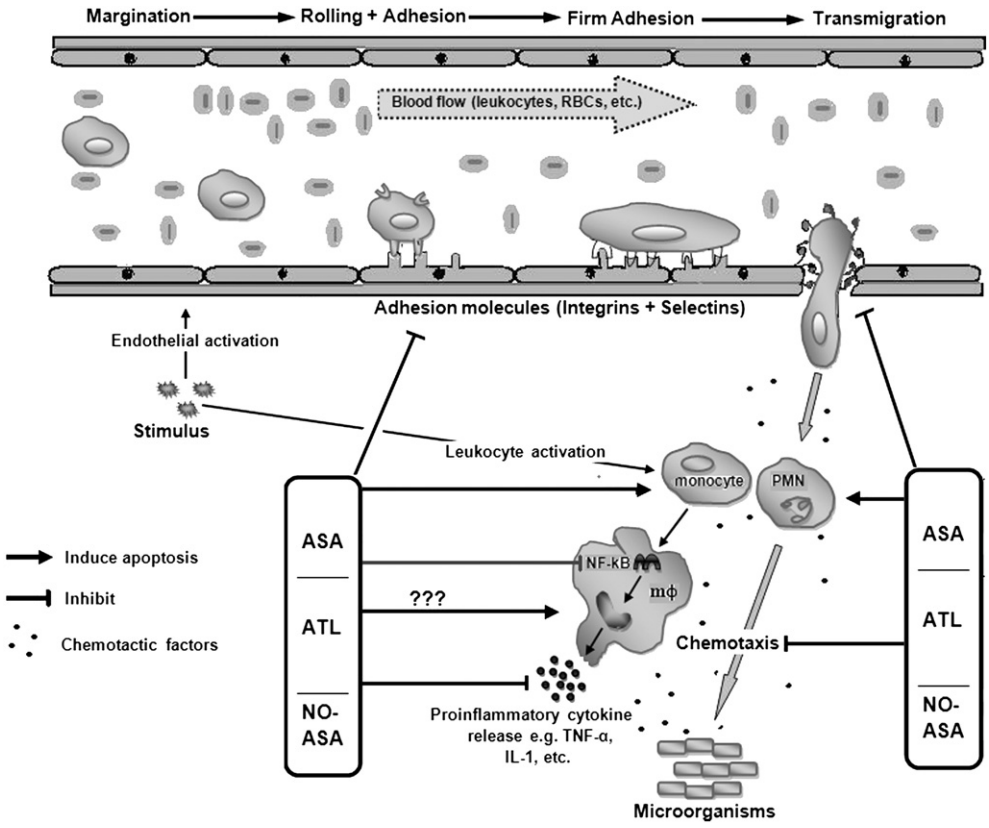

Fig. 1. Immunosuppressant aspects of ASA and its derivatives on different steps of the innate immune-mediated inflammatory reaction. ASA and its derivatives can impede the recruitment cascade of leukocytes by inhibiting their adhesion, transmigration and chemotaxis along with inhibition of proinflammatory cytokine release. ASA induces apoptosis in neutrophils (PMN) and monocytes, but its apoptotic potential against macrophages (mϕ) still remains to be elucidated (???).

derivatives may produce immunosuppressive effects by decreasing the neutrophilic extravasation response linked with the innate immunity.

Another intriguing aspect of the immunosuppressive attributes of ASA against the innate immunity is its ability to induce apoptosis in neutrophils (Fig. 1). In an *in vitro* study, therapeutic concentrations (1–3 mM) of ASA and its metabolite sodium salicylate (NaSal) caused a significant suppression of the NF-kB mediated antiapoptotic proinflammatory signaling that was specifically evoked by LPS and IL-1α in the human neutrophils [50]. In the same study, a direct apoptotic effect was also observed at higher concentrations of ASA [50]. ASA may also weaken the survival of neutrophils because of its unique ability to induce ATLs at therapeutic concentrations. It has been revealed that ATLs can counteract the powerful anti-apoptosis of neutrophils by inhibiting the myeloperoxidase signaling [51], and influencing the apoptosis-delaying action of acute phase reactant serum amyloid A in the human neutrophils [52], thus paving their way to caspase-mediated cell death.

3.2. ASA and macrophages

Macrophages not only share a defensive alliance with neutrophils in the innate immunity [53], but also participate in the regulation of an adaptive-immune attack [54]. After extravasation from blood stream toward the site of infection, they produce cytokines and growth factors of versatile nature and possess a wide array of functional competencies, including antigen presentation, phagocytosis, engulfment of tissue debris, and the immunomodulation [55].

Similar to that of neutrophils, ASA can also inhibit the extravasation of monocytes (Fig. 1). Several experiments in the human and animal settings indicate that ASA can inhibit the tissue recruitment of monocytes/macrophages by impeding their adhesion process through its COX-independent mechanisms. In the human umbilical vein endothelial cells (HUVECs), ASA has been shown to suppress the TNF-α-induced surface expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, through a dose-dependent (1–10 mM concentration range) NF-kB inhibitory mechanism [56]. Similarly, the preincubation of human saphenous vein endothelium with ASA (10 mM) demonstrated a significantly reduced human monocyte adherence *in vitro* by a NO-independent mechanism [57], which suggested that high doses of ASA specifically possess the immunocyte inhibitory potential. The *in vitro* experiments with low-dose ASA (75 mg) in a recent study have also shown the dampened leukocyte/endothelial cell interactions, which resulted in reduced extravascular leukocyte migration and macrophage accumulation [58]. This, nonetheless, was found to be through ASA-triggered, ATL4-induced, antiadhesive NO-dependent mechanism instead of NF-kB inhibition. In the same study, the suppressive effect of ASA (low) on cantharidin-induced topical acute inflammatory responses in humans suggested that ASA may also suppress the innate immune responses at low doses [58]. In an animal study, reduced migratory ability of monocytes due to decreased monocyte/macrophage accumulation and adhesion molecule expression was observed when the New Zealand White rabbits were treated with ASA (10 mg/kg) for 7 days after femoral artery ligation [59]. ASA can also interfere with the chemotaxis of monocytes/macrophages (Fig. 1). In a 3D human coronary model of leukocyte attack (3DLA model), local concentration (5 mM) of ASA inhibited monocyte chemotaxis *in vitro* by 90% [60]. Similarly, a 35% inhibition of monocyte movement (chemotaxis) at therapeutic concentrations of ASA was also interpreted *in vitro* in a prior study [61].

Many of the macrophage-mediated effector mechanisms of innate immunity are elicited via the genetic expression of a diverse array of inflammatory cytokines and chemokines. ASA can inhibit the

macrophage-derived cytokine production through its COX-independent mechanisms (Fig. 1). An investigational study involving murine macrophage cell lines showed that the LPS-stimulated binding of NF-kB to TNF-α promoter site was suppressed at therapeutic doses of ASA, which resulted in the decreased accumulation of TNF-α mRNA and the subsequent protein secretion [62]. Studies of murine macrophage cell lines also show that ASA can inhibit the NO release, a mediator which plays an important role in macrophage-mediated immune regulation. For example, ASA and phenylbutazone caused potent attenuation of NO production from LPS-stimulated RAW264.7 murine macrophage cell lines [63]. Similarly, ASA (3–10 mM concentration range) was described to inhibit LPS- and interferon-gamma (IFN-γ)-stimulated NO production and inducible nitric oxide synthase (iNOS) gene expression in the RAW 264.7 murine macrophage cell lines [64], but this was found to be discrepant with its effect on iNOS mRNA induction in both LPS- and IFN-γ-stimulated cells, which clearly indicated that ASA also intervene some additional pathways related to NO production. A conflicting evidence regarding iNOS expression had also been reported in a prior study [65] in which ASA, NaSal, ibuprofen and indomethacin caused a marked suppression of LPS- and IFN-γ-stimulated iNOS enzyme expression in the rat alveolar macrophages.

Novel NO-donating ASA derivatives can also inhibit the proinflammatory cytokine release from activated monocytes/macrophages (Fig. 1). This has been evidenced by different research groups who focused on NCX-4016 and NCX-4040 (NO-aspirin hybrids) as the main probing agents in their *in vitro* and *in vivo* investigations. The most interesting findings were reported by Fiorucci et al. [66]. They found that NCX-4016 can cause 40–80% inhibition of TNF-α, IL-1β, IL-8, IL-12, IL-18, and IFN-γ release from LPS-challenged human monocytes. In addition, the incubation of human monocytes with NCX-4016 resulted in decreased activity of the caspase-1 (the enzyme required for intracellular processing and maturation of IL-1β and IL-18) through intracellular NO formation [66]. In a later experiment, plasma concentrations of IL-1β and TNF-α were reported to be decreased *in vivo* after an oral treatment of rats with NCX-4016 (90 mg/kg) for 5 days [67]. The suppressive effect of NCX-4016 was also significantly entailed *ex vivo* by the same research group against the release of monocyte chemotactic protein-1 (MCP-1) and IL-6 from the LPS-stimulated human monocytes [68]. In the same study, NCX-4016 was shown to prevent human monocyte activation through inhibition of LPS-induced CD 11b expression. In a similar vein, Minuz et al. described that NCX-4016 (100–300 μM) can reduce TNF-α and IL-6 release from the LPS-challenged adherent human monocytes [69]. Notably, all of the above described cytokine suppressive attributes of NO-donating aspirins were predominantly invoked by their NO-moiety.

A recent finding by Ricciotti et al., however, has demonstrated a NO-independent inhibitory effect of NCX-4040 against cytokine generation [70]. These investigators depicted that micromolar concentrations of NCX-4040 (but not NCX-4016 or aspirin) can decrease the protein expression of TNF-α, IL-1β, IL-10 and IL-18 not only in human whole blood, but also in isolated LPS-stimulated human monocytes *in vitro*. NCX-4040 caused a concentration-dependent indirect inhibition of I-kB degradation and accumulation. A similar result was reported in a prior investigational study [71] that involved novel NO-aspirin hybrid compounds, the existing nitroaspirin (NCX-4016), aspirin, and dexamethasone. The novel NO-aspirin hybrid containing a furoxan NO-releasing group (B8; 10 μM) significantly reduced TNF-α release from LPS-activated human monocytes and macrophages through NF-kB inhibition [71].

In addition to down-regulate the cytokine production, ASA may also interfere with the phagocytic capacity/antigen presentation function of macrophages. One week intraperitoneal treatment of BALB/c mice with ASA (0, 6, 60 mg/kg/day) caused a significant reduction in cell numbers, nonopsonic phagocytosis and immunogenicity of peritoneal macrophages *in vivo* [72]. In the same study, ASA also caused a low-level expression of major histocompatibility complex (MHC)-II molecule, which is crucial for antigen presentation function of macrophages; however, the functional significance of these observations on the opsonic phagocytosis of macrophages remains to be determined.

ASA may induce apoptosis in monocytes, as for instance, ASA and salicylic acid (5 mM) induced a slight apoptotic effect in U-937 myelomonocytic cell lines [73]. Similarly, a comparative *in vitro* evidence for the apoptotic effect of ASA and NO-aspirins (NCX-4016 and NCX-4040) have also been identified in monocytes [74], which suggests that ASA may cause innate immune suppression by inducing apoptosis of monocytes. Nevertheless, its apoptotic potential against resident macrophages still needs clear experimental evidence (Fig. 1).

Contrarily, supportive data from several lines also hint at the immunopotentiating role of ASA and its derivatives toward the monocyte/macrophage-mediated innate responses. It includes: a rise in circulating monocytes in rhinovirus-infected volunteers [75]; increased monocytes/macrophage activation together with CD-11b upregulation [76,77]; potentiation of the LPS-induced TNF-α synthesis in blood monocytes [78–80]; aspirin-triggered lipoxin (ATL)-1-induced monocyte activation and chemotaxis [81], and ATL-stimulated macrophage phagocytosis of apoptotic neutrophils *in vivo* [82].

3.3. ASA and DCs

DCs are the most professional antigen-presenting cells, which produce various proinflammatory cytokines and serve as a bridge between the innate and adaptive immunities [83]. Functionally, antigen sampling/presentation is the cardinal feature of DCs to prime the antigen-specific naïve T cells [84]. ASA can inhibit antigen presentation by DCs and, thus, may reduce their capacity to shape up the subsequent T cell-mediated defensive immune response (Fig. 2). In a recent finding, ASA (at higher doses) inhibited the MHC-I and MHC-II associated antigen presentation in cultured DCs [85]. It impaired the intracellular processing of phagocytosed antigen (ovalbumin), although it could not affect the phagocytic activity and the expression level of total MHC and the co-stimulatory molecules.

DCs express morphologic diversity and have distinct subtypes that originate from both the lymphoid and myeloid lineages. Over the last decade, several *in vitro* and *in vivo* evidence have shown that ASA exerts profound effects on the maturation and differentiation of different dendritic cell phenotypes through its COX-independent mechanisms. It can alter the surface expression of different maturation markers and costimulatory molecules on the immature DCs and, thus, can inhibit their subsequent immunostimulatory function (Fig. 2). For example, high-dose ASA (2.5 mM) inhibited the terminal differentiation of immature human myeloid DCs *in vitro* which, in turn, restricted both their maturation and the function to stimulate T cell proliferation. It suppressed the phenotypic expression of surface marker CD83 and the secretion of IL-12p40 through its NF-kB inhibitory mechanism [86]. Similarly, a high dose-dependent inhibitory effect of ASA was also examined against *in vitro* maturation of murine bone marrow-derived myeloid DCs, which were stimulated by granulocyte/macrophage colony-stimulating factor (GM-CSF) plus IL-4 [87]. ASA caused a significant suppression of CD40, CD80, and MHC-II expression by targeting the NF-kBp50 pathway, while CD11c and MHC-I expression remained unaffected. DCs that were matured in the presence of ASA showed reduced immunoproliferative ability toward naïve allogeneic T cells because of the decreased IL-12 and IL-10 production. Moreover, the capacity of responding T cells to produce IL-2 was also decreased. In the same experiment, the immunostimulatory function of ASA-treated DCs, which were pulsed with the hapten trinitrobenzenesulfonic acid, was also inhibited *in vivo* [87].

High-dose ASA can also impede the maturation of monocyte-derived DCs (MoDCs). In a comparative study, sub-apoptotic

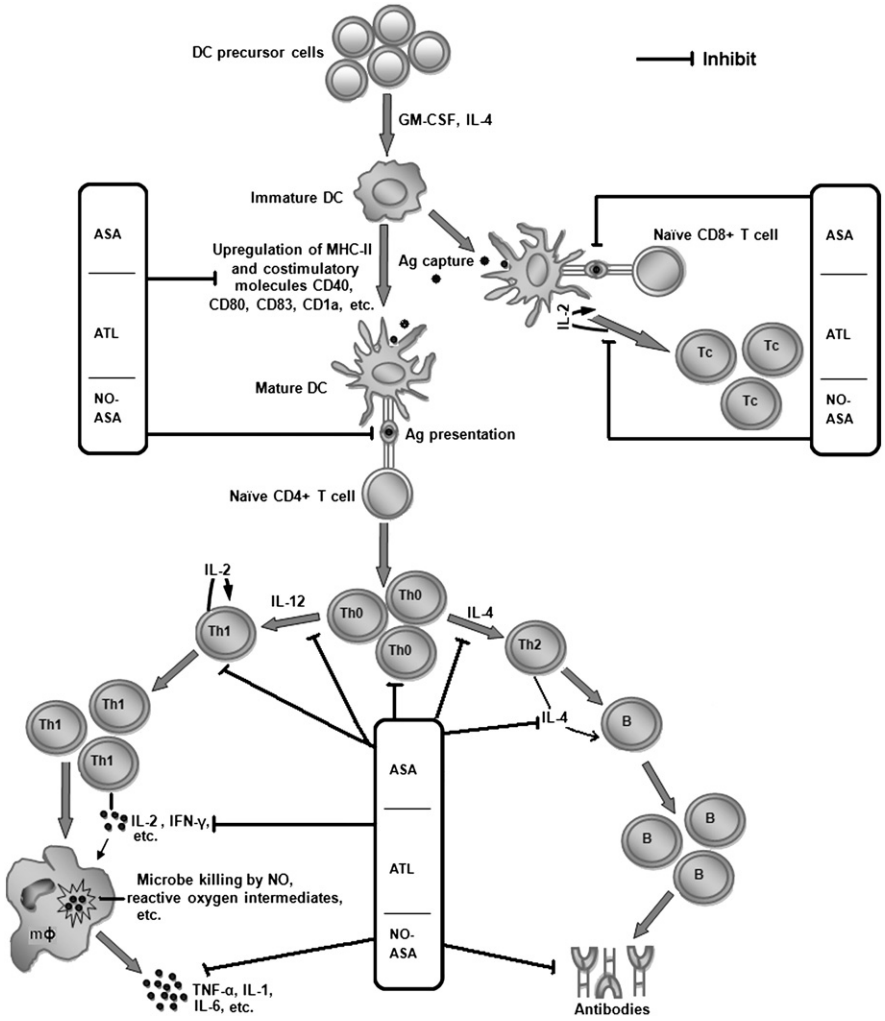

Fig. 2. Illustration of the immunosuppressant mechanisms of ASA and its derivatives during induction and effector phases of the innate and adaptive immunities. ASA and its derivatives inhibit the maturation/differentiation process of dendritic cells (DCs) by decreasing the surface expression of various maturation markers, and can also suppress their T cell immunostimulatory power by decreasing the antigen (Ag) presentation capacity. In case of T and B lymphocytes, ASA and its derivatives suppress the cytokine production (particularly IL-2, IL-4, etc.), decrease their proliferation/differentiation, and inhibit antibodies secretion from B cells.

concentrations of ASA (2 mM), NCX-4016 (200 μM), and NCX-4040 (2 μM) impaired the differentiation, maturation and allostimulatory activity of LPS-stimulated MoDCs *in vitro* [74]. Both ASA and the NO-ASA derivatives decreased the expression of surface markers and the co-stimulatory molecules in MoDCs, while the production of IL-10 and IL-12p40 was reduced in particular by ASA. In addition, the demonstration of the apoptosis-stimulating concentrations of ASA (4–8 mM), NCX-4016 (400–800 μM), and NCX-4040 (4–8 μM) by Bufan et al. [74] suggests that they may also exert a direct apoptotic effect on MoDCs. Of note, ASA was also reported to suppress the LPS-induced maturation of MoDCs at therapeutic concentrations by inhibiting the surface expression of co-stimulatory molecules together with a decrease in IL-10 and IL-12 production [88]. These findings, including the decreased expression of co-stimulatory molecules and the altered cytokine production from ASA-treated DCs as well as the DCs-stimulated T cells, may provide the basis for the potential implication of ASA-treated DCs to induce immunologic tolerance (Fig. 3) [89].

Furthermore, native and aspirin-triggered lipoxins were reported to inhibit the proinflammatory cytokine release from DCs through activation of the suppressor of cytokine signaling-2 (SOCS-2) expression [90]. Later on, the ATL-induced SOCS-2 expression and the SOCS-2-dependent ubiquitinylation were entailed to ASA's lipoxin-derived control of DCs-mediated innate immunity [91].

Summarily, the above described suppressive effects of ASA against the maturation process as well as the subsequent immunostimulatory activity of DCs suggest its immunosuppressant potential against the innate and adaptive immune responses.

3.4. ASA and NK cells

NK cells are a type of cytotoxic lymphocytes endowed with a unique ability to kill a variety of target cells (tumor cells, virally infected cells, IgG-opsonized cells) regardless of their MHC expression. They play an important role at the interface between the innate and adaptive immunities [92].

The immunoregulatory potential of ASA with respect to NK cells has not been studied widely. An apparent discrepancy about the ASA-mediated modulation of NK cell activity, however, was reported in the two old studies. Initially, ASA was shown to cause 80–100% suppression of the melanoma-induced NK cell activity at a single therapeutic dose of 660 mg in tumor patients [93], but in a later *in vitro* experiment, ASA did not affect the spontaneous or the IFN-β-stimulated NK cell activity [94]. This apparent inconsistency indicates that further studies ought to be endorsed to shed light on the yet underexplored role of ASA against the NK cells.

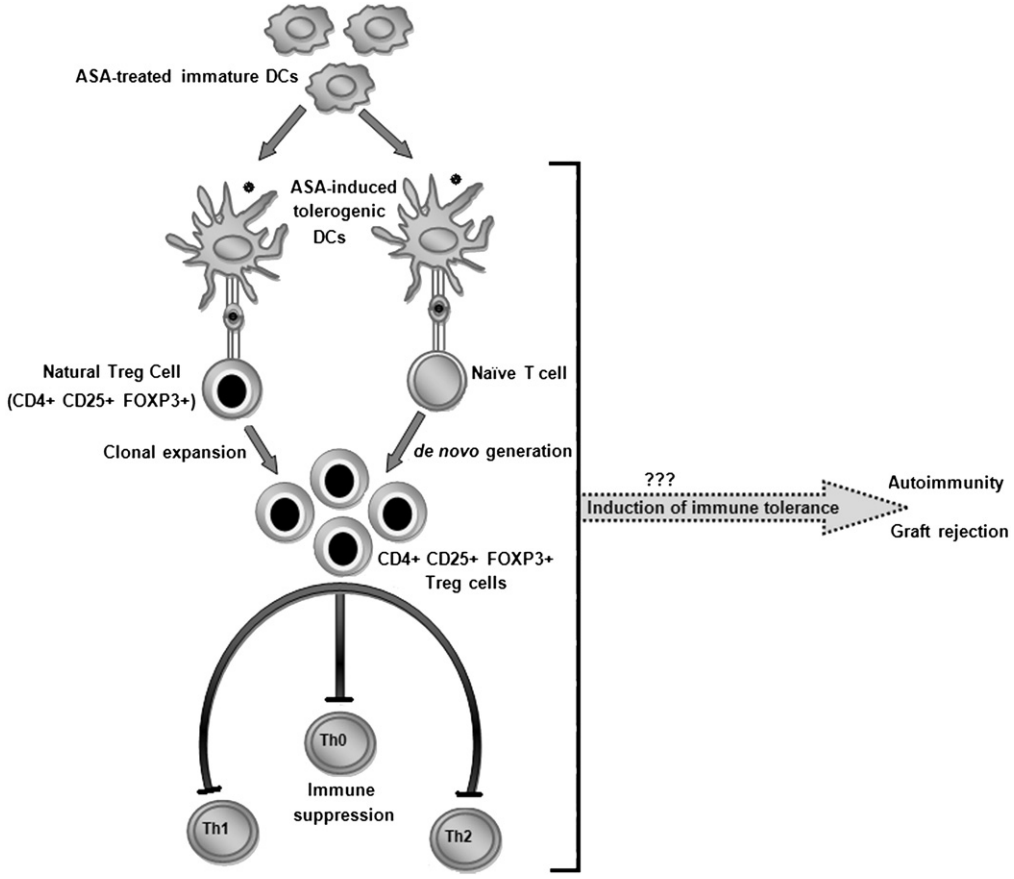

Fig. 3. ASA and the induction of immune tolerance. ASA can induce tolerogenic activity in DCs, which in turn causes not only the clonal expansion of natural Treg cells (CD4+ CD25+ FOXP3+), but also their *de novo* generation from naïve T cells. The immunotherapeutic exploitation of ASA-induced/enhanced Treg cells activity may have potential implication (???) to induce immune tolerance against autoimmunity and transplant rejection.

3.5. ASA and T effector cells

T lymphocytes are mastered to regulate the adaptive immune response against different protein antigens. In addition to direct the diverse elements of cell-mediated immunity, they also play a key role in the induction of B cell-derived humoral immunity.

Tissue recruitment of T lymphocytes is a crucial step of the cell-mediated adaptive immune response. The relevant *in vitro* and *ex vivo* findings indicate that ASA and NaSal can disrupt the integrin- and L-selectin-mediated binding of T cells to the endothelium both under static and non-static conditions [95,96]. In addition, ASA reduced the adhesion of jurkat T cells to IL-1β-stimulated human aortic smooth muscle cells. It suppressed the NF-kB activity in a dose-dependent manner that resulted in the decreased expression of ICAM-1 and VCAM-1 [97]. ASA (5 mM) also caused a slight reduction in ICAM-1 upregulation along with 50% inhibition of CD4+ T lymphocyte adherence in 3DLA model [60]. These findings indicate that ASA may impede the tissue recruitment of T cells by interfering with the adhesion and transmigration processes and, thus, may control T cell-mediated intravascular as well as the extravascular adaptive immune disorders.

ASA can also exert the direct suppressive effects on the T cell activation or proliferation (Fig. 2). Treatment of BALB/c mice with low or high doses of ASA for 4 consecutive weeks showed a significant decrease in the percentage and number of CD4+ T cells in the periphery [98]. Moreover, ASA inhibited the T cell activation in the ovariectomy-induced osteoporosis mouse model [99], reduced lymphocyte viability in cell culture [100], and caused dose-dependent attenuation of concanavalin A (Con A)-stimulated CD4+ T cells as well as the IL-2-induced CD8+ CTLL-2 (a murine cytotoxic T cell line) proliferation [63]. ASA also caused dose-dependent inhibition of T lymphocytes proliferation in the human peripheral blood mononuclear cells (PBMCs) by arresting their growth in the Go/G1 phase [73]. A relevant Go/G1 cell cycle arrest in jurkat T cells was also reported in a later study in which ASA (5 mM) was proposed to inhibit their growth through beta-catenin independent mechanisms [101]. In vitiligo, increased serum concentrations of the immunologic markers, such as vitiligo antibodies (V-IgG) and soluble IL-2 receptors (sIL-2R), indicate the intensified humoral and cellular immune responses. ASA caused a significant reduction in the serum concentrations of V-IgG and sIL-2R of the active vitiligo patients that were treated at a single oral dose of 300 mg for 12 consecutive weeks [102], which indirectly suggests its immunosuppressive potential against T cell-mediated immunity. Similarly, the treatment of adenovirus-infected mice with low dose ASA and clopidogrel resulted in reduced homing of virus-specific cytotoxic T cells [103], which further indicated that low-dose ASA can also suppress T cell activation. Moreover, ASA has been described to induce apoptosis in jurkat T cells through alteration of the Mcl-1/Noxa balance [104]. A prior study [105] that was conducted in digestive tract tumor cell lines also suggested that ASA can augment apoptosis ratio in human gammadelta T cells if its concentration exceeds 3.2 mM. Notwithstanding, ASA enhanced cytotoxic effect of gammadelta T cells at the routine clinical concentration range (0.4 mM to 0.8 mM).

ASA and its derivatives can inhibit the cytokine production related to the T cell-mediated adaptive immune response (Fig. 2). For instance, ASA and ATL analogs can down-regulate the production of different cytokines such as IL-1β, IL-12, IL-18, IFN-γ, and TNF-α from PBMCs [73,106,107]. NCX-4016 inhibited the Th1-like response by decreasing the cytokine/chemokine production in Con A-induced T

cell-mediated liver injury [66]. NCX-4016 also induced metabolic hypoxia in CD3/CD28-costimulated lymphocytes which, in turn, can limit lymphocyte reactivity to costimulatory molecules [108].

IL-4 plays a critical role in the humoral and adaptive immunities by up-regulating the Th2-type immune responses. At therapeutic concentration range, ASA caused a substantial decrease in IL-4 production and its mRNA expression in freshly isolated and mitogen-primed human CD4+ cells, while it could not affect IL-13, IFN-γ, and IL-2 expression [109]. Notably, the ASA-caused suppression of IL-4 transcription was not mediated through its previously established NF-kB inhibitory mechanism [12], rather, it was postulated to be through a yet unestablished mechanism that features the decreased binding of an inducible factor to an IL-4 promoter region. Altogether, the above described observations imply an immunosuppressant role of ASA for T cell-mediated adaptive immunity.

Conversely, collateral evidences from prior research indicate that ASA may promote T cell function by increasing their activation or proliferation [110–114]. This is also worthy of note that ASA can induce IFN-γ production typical of T cell phenotypes [115–117], which suggests that ASA may enhance T cell effector responses. On the other hand, some evidences from prior research also indicate that ASA could not affect lymphocyte proliferation or viability [118–121].

3.6. ASA and Treg cells

Treg cells are a functionally distinct subpopulation of T lymphocytes that are specialized for immune suppression. It is widely accepted that naturally occurring Treg cells (CD4+ CD25+ FOXP3+ Treg cells) have a critical role in the maintenance of immunologic self-tolerance and the immune homeostasis. Their depletion can result in a variety of autoimmune disorders and anti-graft responses [122]. Surprisingly, ASA can enhance the number of natural Treg cells (Fig. 3), as for example, a study in BALB/c mice showed that ASA can selectively augment the percentage and number of CD4+ CD25+ FOXP3+ Treg cells [98]. Importantly, the ratio of their functional population was significantly increased at the therapeutic dose range of ASA.

In addition, ASA may also enhance Treg cell number/function indirectly (Fig. 3). ASA possesses the ability to induce tolerogenic activity in DCs which, in turn, can induce regulatory function in the responder naive T cells [123]. ASA-induced tolerogenic DCs express decreased costimulatory ability and an upregulated expression of immunoglobulin-like transcript-3, a co-inhibitor of T cell activation required to induce Treg cell activity [89]. ASA-induced tolerogenic DCs can also stimulate *de novo* generation of Treg cells, particularly the CD4+ CD25+ FOXP3+ Treg cells (Fig. 3). Studies by Buckland et al. revealed that ASA-induced tolerogenic DCs can induce hyporesponsiveness and regulatory activity in responder naïve and memory T cells through involvement of both the cell–cell contact and the inhibitory cytokine activity [124,125]. In accordance with these findings, a later study by Hernandez et al. also showed a marked decrease in the production of Th1-cytokines, IL-2 and IFN-γ, after stimulation of T cells by ASA-treated DCs [126]. Of note, the blockade of NF-kB signaling pathway was proposed to be the cause of Treg cell generation.

In summary, ASA may indirectly cause immune suppression by enhancing the Treg cell activity/function directly or via its ability to induce tolerogenic DCs which, then, subsequently induce regulatory activity in responder naive T cells, or cause *de novo* generation of Treg cells.

3.7. ASA and B cells

Antigen-induced antibody secretion from plasma B cells is fundamental to the humoral immune response. ASA can suppress the antibody-mediated humoral immune response (Fig. 2). Different lines of evidence suggest that ASA can weaken the host defense including: a decrease in the synthesis of IgM and IgG antibodies in the stimulated human PBMCs [127]; a gradual fall in serum IgA levels of juvenile rheumatoid arthritis patients [128]; suppression of the T cell-dependent antibody response in juvenile males of the pregnant Sprague–Dawley rats [129], and reduction in the serum V-IgG activity of active vitiligo patients [102]. ASA also suppressed the serum neutralizing antibody response in a double-blind placebo-controlled trial [75].

Further evidence shows that ASA induced apoptosis of B chronic lymphocytic leukemia cells via COX-independent mechanisms that involve activation of caspases, thus resulting in DNA fragmentation together with proteolytic cleavage of poly (ADP-ribose) polymerase [130]. Similarly, NO-ASA induced apoptosis in human B-lymphoblastoid TK6 cells through oxidative stress that involves induction of H2AX phosphorylation, an effect possibly dependent on its NO moiety [131]. ASA has also been manifested to diminish the viability of Epstein–Bar Virus-positive B lymphocytes because of its unique ability to downregulate the intracellular NF-kB(p65) activity in the nucleus and, thus, induced Epstein–Bar Virus lytic replication [132]. In contrast, ASA could not affect the primary humoral response in rabbit peripheral blood [133].

4. Clinical prospects of ASA with respect to the immunopathologic response in autoimmunity, allograft rejection, and immunotolerance

The last several years of immunology-based scrutinies of ASA have produced a great interest in, and the data about, its immunotherapeutic implication against the immunopathologic responses. In autoimmunity, ASA has a long-lasting remedial respect for rheumatoid arthritis, although the majority of contributing data has been addressed primarily by population studies. Experimentally, ASA was reported to inhibit the anti-type II collagen antibody formation not only in type II collagen-induced arthritis in rats [134], but also in the adjuvant arthritis [135]. ASA also caused a gradual decrease in serum antibody levels of juvenile rheumatoid arthritis patients [128], which suggests that ASA may suppress the humoral immune response in arthritis. Moreover, ASA induced apoptosis in rheumatoid synovial cells by causing DNA fragmentation, which was then followed by their suppressed proliferation and reduced viability [136]. In another study, ASA and celecoxib exhibited therapeutic efficacy against the autoimmune murine model of systemic lupus erythematosus. The intermittent pulse therapy with ASA and celecoxib caused a significant inhibition of autoantibodies production and T cell response through the COX-II inhibitory mechanism [137].

Autoimmune atherosclerosis can evoke both the autoreactive T cell responses and the autoantibodies production [138,139]. Though a clear-cut evidence to support an ASA-mediated immunosuppression against autoimmune atherosclerosis is yet unexplored, it was shown to suppress T cell-mediated response in HUVECs model. ASA caused dose-dependent inhibition of T cells proliferation as well as the TNF-α-stimulated, NF-kB-mediated expression of adhesion molecules, such as MCP-1 and the heat shock protein 60, which is a key player in early stages of autoimmune atherosclerosis [140]. In addition, ASA has been reported to prevent the steering mechanism of atherosclerosis development by reducing NF-kB-mediated expression of ICAM-1 and VCAM-1, thereby decreasing T cell adhesion to IL-1β stimulated aortic smooth muscle cells [97].

In addition to the immunosuppressive capability against autoimmunity, ASA may also express therapeutic relevance to graft-rejection. There is some evidence which supports the importance of ASA related to survival of allogeneic cardiac allografts in murine models on one hand [141,142], and the substantial improvement of renal allograft function and survival in kidney transplantation on the other [143]. The local application of ASA also reduced vein graft

arteriosclerosis through endothelial protection [144], which indicates its importance in vein grafts.

The more striking evidence for the immunosuppressive potential of ASA in autoimmunity or allograft rejection emerged during the last decade when ASA was apparently demonstrated to induce and/or expand Treg cell function, especially the CD4+ CD25+ FOXP3+ Treg cells (Fig. 3) [89,98,124,125]. Mounting evidence indicates that immunosuppressive traits of Treg cells, in particular the FOXP3+ Treg cells, are critical for the induction and maintenance of immunologic tolerance [145,146]. Therefore, the current dogma in scientific community is to manipulate the Treg cell-mediated immunosuppression as an immunotherapeutic option against unwanted immune responses that are a characteristic of autoimmune disorders or allograft rejection. In short, augmentation of Treg cell function by ASA-based effective immunotherapy might help the medical community to treat allograft/autoimmune diseases in future. However, the details for a definite clinical perspective are yet to be worked out.

5. ASA and the immune-hypothalamic–pituitary–adrenal axis

The bidirectional communication between the immune and neuroendocrine systems can activate the hypothalamic–pituitary–adrenal (HPA) axis that plays a key role in subserving the body's response to different stimuli including stress (physical or psychological) and the inflammatory mediators (such as cytokines and PGs), thereby maintaining the homeostatic balance via the neuroendocrine hormonal release (e.g. adrenal glucocorticoids) [147–149]. Compelling data emerging from prior research now indicates that alterations in neuroendocrine hormonal release from HPA axis may also possess immunoregulatory impacts on the immune system, particularly, in restraining or shaping the immune responses in a variety of inflammatory/autoimmune conditions [150–153]. Pharmacologically, activity of HPA axis can be altered by a variety of drugs having different mechanisms of action, including ginkgo biloba [154,155], ethanol [156], and COX inhibitors [157–159]. ASA was shown to augment the effects of naloxone [160] and to inhibit those of vasopressin [161] upon the hormonal secretion (ACTH and cortisol) from the HPA axis, which were suggested to be mediated by its COX-inhibitory mechanism affecting the synthesis of endogenous PGs that play an important role in the inflammation-induced activation and responsiveness of HPA axis [162,163]. This implies that ASA may also cause immunomodulation by indirectly affecting the neuroendocrine hormonal release through alteration of HPA activity and its subsequent immunoregulatory impact on the immune system. Nevertheless, further interventional studies ought to be endorsed in order to distinctly define the immunomodulatory associations between ASA and the HPA responsiveness with respect to inflammatory and autoimmune conditions.

6. Concluding remarks and future dimensions

This review clearly describes the immunomodulatory potential of ASA and its derivatives. ASA exerts multiple effects on different components of innate and adaptive immunities. It can induce apoptosis in different immune cells, modulate their proliferation/maturation process, regulate their cytokine production, and can also trigger a lipoxin-driven immune counter-regulation. Together with this, the immunosuppressive capability of ASA through induction of tolerogenic DCs and then subsequent uprising of Treg cells is the most spectacular aspect of its immunopharmacological attributes. As shown in Fig. 3, we conceive that immunotherapeutic exploitation of ASA-induced tolerogenic DCs/Treg cells may facilitate the development of strategies that not only clonally expand natural Treg cells, but would also recruit and differentiate naïve T cells to express regulatory activity at graft-site, thereby restricting the culpably active and expanding T effector cells. This may definitely help to augment the immunologic tolerance against transplant rejection. Furthermore, the ASA-based immunotherapeutic approach may also be employed to harness immune tolerance against a diverse range of autoimmune as well as the autoinflammatory conditions. We hope that ongoing future revelations in this regard will enable the medical community to substitute ASA-based immunotherapeutic implications in place of traditionally used immunosuppressant agents (like corticosteroids) in certain clinical settings, including autoimmunity and transplant rejection.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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