Published in final edited form as:

Curr Opin Lipidol. 2019 June ; 30(3): 218–223. doi:10.1097/MOL.0000000000000596.

Regulation of lipid rafts, angiogenesis and inflammation by AIBP

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Abstract

Purpose of review: Recent studies demonstrate an important role of the secreted apolipoprotein A-I binding protein (AIBP) in regulation of cholesterol efflux and lipid rafts. The article discusses these findings in the context of angiogenesis and inflammation.

Recent findings: Lipid rafts are cholesterol- and sphingomyelin-rich membrane domains where many receptor complexes assemble upon activation. AIBP mediates selective cholesterol efflux, in part via binding to TLR4 in activated macrophages and microglia, and thus reverses lipid raft increases in activated cells. Recent papers report AIBP regulation of VEGFR2, Notch1 and TLR4 function. In zebrafish and mouse animal models, AIBP deficiency results in accelerated angiogenesis, increased inflammation and exacerbated atherosclerosis. Spinal delivery of recombinant AIBP reduces neuraxial inflammation and reverses persistent pain state in a mouse model of chemotherapy-induced polyneuropathy. Inhalation of recombinant AIBP reduces LPS-induced acute lung injury in mice. These findings are discussed in the perspective of AIBP's proposed other function, as an NAD(P)H hydrate epimerase (NAXE), evolving into a regulator of cholesterol trafficking and lipid rafts.

Summary: Novel findings of AIBP regulatory circuitry affecting lipid rafts and related cellular processes may provide new therapeutic avenues for angiogenic and inflammatory diseases.

Keywords

cholesterol; lipid rafts; angiogenesis; inflammation; apoA-I binding protein

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Conflicts of Interest

L.F. and Y.I.M. are authors of patent applications relevant to the topic of this article. Y.I.M. is a co-founder of Raft Pharmaceuticals.

Introduction

Apolipoprotein A-I binding protein (AIBP), encoded by the *APOA1BP* gene, was first identified in a yeast two-hybrid screen as a binding partner of human apoA-I [1], hence the name. AIBP is ubiquitously expressed in mice and humans, with high expression levels in the brain, kidney, liver, and reproductive organs. Although AIBP is constitutively expressed, its secretion but not mRNA expression is enhanced in kidney-derived HEK293 cells following incubation with apoA-I or HDL [1] and in alveolar macrophages following stimulation with LPS [2]. AIBP protein can be detected in the cerebrospinal fluid and urine of healthy individuals, whereas its expression in plasma was found only in patients with sepsis[1].

Since the original discovery of AIBP, many different functions have been attributed to the protein, ranging from involvement in NAD(P) and vitamin B6 metabolism to regulation of cholesterol efflux and lipid rafts. This article will discuss recent findings concerning AIBP biology, in the context of its expression in different organisms and under pathological conditions.

Involvement in NAD(P) and vitamin B6 metabolism

Recently, the *APOA1BP* gene was renamed in genomic databases as *NAXE* because the AIBP protein was found to have a surprising enzymatic activity of an NAD(P)H hydrate [NAD(P)HX] epimerase. NAD(P)H can be converted into a hydrated form, NAD(P)HX, by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) or spontaneously at high temperatures or acidic pH [3]. NAD(P)HX exists in the form of R and S epimers. The epimerase facilitates epimer interconversion, but only the S epimer is converted back to NAD(P)H by a dehydratase [4, 5]. If left unrepaired, the R and S NAD(P)HX will form a cyclic metabolite, which is toxic and inhibits dehydratase activity [6, 7]. However, even though NAXE is highly conserved, in the absence of NAXE, *E. coli*, yeast, plants or mice show no apparent defects in growth [8-16], suggesting that the NAD(P)HX epimerase function may be redundant. In agreement, in an NAXE epimerase-dead bacteria mutant, the levels of R, S, and cyclic NAD(P)X are comparable to those in wild type controls [14]. Although higher temperature increases cellular NAD(P)HX content, temperature seems to have no apparent effect on the growth of NAXE-deficient organisms [14]. Thus, the in vivo physiological significance of the NAXE enzymatic activity and the toxicity of cyclic NAD(P)HX are yet to be determined.

In bacteria and archaea, the NAXE protein is fused with the dehydratase, which may facilitate the repair of NAD(P)HX [17, 18]. However, in plants, NAXE is fused with a different enzyme, pyridoxamine phosphate oxidase (PPOX), which is required for vitamin B6 synthesis. In plant cells, NAXE can be localized in the cytosol or in the chloroplast, depending on whether or not its isoforms have a chloroplast-targeting signal [10]. In addition to its putative role as an epimerase, NAXE genes are clustered with B6 metabolism-associated genes on the same chromosome in yeast and in *A. thaliana* [14]. Furthermore, loss or mutation of NAXE orthologue in *E. coli*, where NAXE is fused with dehydratase, reduces B6 content and changes amino acid-associated metabolism [14]. However, vitamin

B6 cannot be synthesized in humans [19], thus the biological function of NAXE in mammals may be dissociated from B6 metabolism or associated with other functions as discussed below. In vertebrate animals, NAXE is expressed as an independent protein, dissociated from either dehydratase or PPOX.

In humans, AIBP loss-of-function mutations confer a lethal neurometabolic phenotype in infants [20, 21]. One possibility is that, unlike mice in which loss of AIBP does not affect viability [15, 16], humans are less tolerant to the toxic effects of cyclic NAD(P)HX compared to other organisms. The other possibility, however, is that NAXE's major function has changed in humans and other vertebrates. As shown in the original AIBP study [1] and later confirmed [22], AIBP/NAXE can bind apoA-I, the protein that does not exist in bacteria or plants. As apoA-I and other elements of lipoprotein metabolism emerge in evolution, NAXE – by virtue of apoA-I and HDL binding and of being a secreted protein – may have become involved in regulation of cholesterol trafficking, justifying its original AIBP designation.

Regulation of lipid rafts via cholesterol efflux

Lipid rafts are dynamic plasma membrane microdomains enriched in cholesterol and sphingolipids that serve as receptor signaling platforms. Activation of many receptors depends on the clustering and abundance of lipid rafts, where receptors dimerize/oligomerize to initiate signaling [23-29]. Cholesterol removal from lipid rafts disrupts receptor signaling [30]. Treatment with β -cyclodextrins is a common method to deplete cholesterol from the plasma membrane in cell culture experiments, which does result in inhibition of receptor-mediated responses [31, 32]. Cyclodextrin derivatives given systemically or intrathecally are being developed as a promising therapy for the Niemann-Pick type C disease, a severe neurodegenerative lysosomal cholesterol storage disorder [33-36].

However, the physiologic mechanism of cholesterol removal from the cell involves the membrane and endosomal ATP-binding cassette (ABC) cholesterol transporters ABCA1 and ABCG1 and the extracellular cholesterol acceptors lipid-poor apoA-I and the HDL, whose major protein is apoA-I [37-39]. In ABCA1/ABCG1-deficient cells, there is a substantial increase in inflammatory gene expression mediated by lipid raft-dependent TLR4 signaling [40, 41]. The cholesterol acceptors HDL and lipid-poor apoA-I and a number of apoA-I mimetic peptides reduce TLR4-mediated inflammatory responses as well [42-47]. Yet, these mechanisms of cholesterol efflux do not imply any spatial or tissue selectivity, and the indiscriminate character of cellular cholesterol depletion by cyclodextrins or by apoA-I may limit their applications.

Regulation of angiogenesis by AIBP

Work from authors' laboratories demonstrates that AIBP accelerates cholesterol efflux from endothelial cells (ECs) to HDL [22]. By itself, AIBP does not promote cholesterol efflux in the absence of apoA-I or HDL. Rather, AIBP binding to cells increases the overall capacity of the cell to bind HDL and increases the rate of HDL dissociation from cells [22], thereby

creating conditions that facilitate cholesterol efflux. This achieves a robust biological effect on angiogenesis. Mechanistically, AIBP-mediated cholesterol efflux disrupts lipid rafts, which are required for the dimerization and endocytosis of cell surface vascular endothelial growth factor receptor-2 (VEGFR2) in ECs, thereby impairing VEGFR2 signaling and impeding angiogenesis. The inhibitory effect of AIBP on angiogenesis is achieved by two mechanisms, in which one is to impair proangiogenic VEGFR2 signaling, and the other is to augment anti-angiogenic Notch signaling [15] (Fig. 1). For Notch activation, AIBP-mediated lipid raft disruption relocates Notch and the protease γ -secretase, which cleaves Notch for its activation, from lipid rafts to non-raft membrane regions, thereby elevating their co-distribution and subsequent Notch activation [15]. Increased levels of cholesterol acceptors apoA-I and HDL in transgenic mice can achieve similar effect on neovessel formation as AIBP does, which may be due to the fact that a prolonged exposure to cholesterol acceptors have similar effect on lipid raft disruption [15].

Regulation of inflammation by AIBP

Similar to accelerating cholesterol efflux from ECs [22], AIBP augments cholesterol efflux from macrophages and microglia [2, 16, 48, 49]. One mechanism involves AIBP-mediated stabilization of ABCA1 protein and prevention of its degradation via the ubiquitination pathway [48]. As with the VEGF-induced activation state in EC, effect of AIBP on cholesterol efflux is much stronger in macrophages/microglia stimulated with LPS than in non-stimulated cells [2, 49]. One reason for this effect in cells of the myeloid lineage is that AIBP binds to TLR4 [49]. LPS impedes cholesterol efflux mechanisms, resulting in increased levels and clustering of lipid rafts [50, 51]. Furthermore, TLR4 localization to lipid rafts increases in activated cells. Thus, increased surface expression of TLR4 leads to selective AIBP binding – and targeting cholesterol efflux – to activated inflammatory cells. AIBP has little effect on non-activated cells [49]. The structural determinants of AIBP-TLR4 interaction are yet unknown. In addition, AIBP may have other than TLR4 binding partners in non-myeloid cells.

AIBP-mediated reversal of LPS-induced lipid rafts abundance and clustering inhibits raft-dependent dimerization of TLR4 (Fig. 2) and its downstream signaling: AIBP inhibits LPS-induced phosphorylation of NF κ B p65 and MAP kinases ERK1/2 and p38, the effect reversed by adding cholesterol back to the plasma membrane, and the expression of inflammatory cytokines [2, 16, 49, 52].

Neuraxial inflammation, in large part due to TLR4-activated microglia, is often a causative factor in the development of neuropathic pain [53-55]. TLR4 knockout mice do not develop mechanical allodynia (pain response to a light touch, which normally is not perceived as a painful stimulus) in models of poly and mono neuropathy [53-55]. Intrathecal injections of recombinant AIBP reverse LPS-induced increases in lipid rafts and TLR4 dimerization in spinal microglia. Remarkably, intrathecal AIBP prevents and reverses not only LPS-induced allodynia but also chemotherapy (e.g., cisplatin) associated persistent pain state [49]. It remains unclear what cholesterol acceptors AIBP interacts with in the CNS. ApoA-I is not expressed in the brain, and peripheral blood lipoproteins do not cross the blood-brain barrier, although active transport of lipid-free apoA-I from the periphery to the brain has been

described [56, 57]. Still, apoA-I is a minor component of CNS HDL, with apoE expressed by astrocytes being a major apolipoprotein in adult brain [57, 58].

HDL may not be the sole cholesterol acceptor whose function AIBP augments. In the HDL-devoid pulmonary airspace, surfactant, which is a lipoprotein, can promote cholesterol efflux from alveolar macrophages [2]. AIBP binds a structural component of surfactant, surfactant protein B (SP-B), augments cholesterol efflux from alveolar macrophages to surfactant, and reverses LPS-induced increases in lipid raft content [2]. In a mouse model of acute lung injury, inhaled recombinant AIBP significantly reduces LPS-induced recruitment of polymorphonuclear leukocytes, secretion of IL-6 and leakage of plasma proteins in the lung [2]. Inhalation of recombinant AIBP likely reinforces an innate protective mechanism: an increased lung expression of endogenous AIBP characterizes acute lung injury, both in a mouse model and in human patients with acute respiratory distress syndrome (ARDS) [2].

Regulation of lipid metabolism and atherosclerosis by AIBP

Loss of AIBP in western diet (high-cholesterol and high-fat) fed LDLR knockout mice manifests in greater liver steatosis, glucose intolerance, increased VLDL production and exacerbated atherosclerosis [16]. All these changes may be attributed to fat-induced dysregulated lipoprotein metabolism in the liver and the elevated systemic inflammation because the *Ldlr*^{-/-} *Apoa1bp*^{-/-} mice fed a high-cholesterol but normal-fat diet, which does not instigate obesity and metabolic syndrome [59], show no difference in lipoprotein levels or atherosclerosis compared to *Ldlr*^{-/-} mice [16]. AIBP gain-of-function, delivered by adeno-associated virus, reduces liver steatosis and documents a profound anti-inflammatory and atheroprotective effects in mice [16, 60], which is likely conferred by enhanced cholesterol efflux. Similarly, induced *Aibp* overexpression in zebrafish reduces vascular lipid accumulation [16]. In mouse studies, weight gain of *Apoa1bp*^{-/-} mice was associated with expansion of visceral adipose tissue. It remains unclear whether the liver and/or the adipose tissue, two critical organs in regulation of lipid metabolism, precipitate metabolic abnormalities in the absence of AIBP.

Conclusions and outstanding questions

This article highlighted multiple functions of the AIBP protein, from NAD(P)HX epimerase activity to involvement in vitamin B6 metabolism to regulation of cholesterol efflux and lipid rafts. The in vivo significance of each of these functions seems to change depending on whether AIBP is expressed in bacteria, yeast, plants or vertebrate animals. *Apoa1bp* knockout as well as gain-of-function studies in mice and zebrafish point to the significance of AIBP regulation of cholesterol efflux and lipid rafts manifesting in control of angiogenesis and inflammation.

Since deregulated angiogenesis and inflammation are associated with a wide variety of diseases, conceivably, the applications of AIBP, its mimetics, agonists or antagonists will guide new therapeutic strategies, either as a stand-alone therapy or in combination with current treatment regimens. While progress has been made to elucidate the role of AIBP in angiogenesis, inflammation, and NAD(P)H and B6 metabolism, much work is needed to

fully understand the effects of AIBP loss-of-function and gain-of-function in human disorders. It remains unclear whether NAXE's NAD(P)HX repair function plays an important role in higher organisms or becomes redundant. Although NADH is essential for lipid metabolism, NADHX only constitutes ~1% of total NADH levels [14], which makes it unlikely to establish a causative connection between NAXE enzymatic activity for NADHX recycling and lipid metabolism. But it is possible that the toxic cyclic NAD(P)HX underlies some of the defects observed in patients [61]. Although AIBP functions in a paracrine fashion, it is also expressed in ECs. Thus, the questions remain: Would AIBP also act cell-autonomously in ECs? In addition to TLR4, what are other cell surface binding partners of AIBP defining its selective regulation of cholesterol efflux and lipid rafts and, by extension, selective regulation of angiogenesis and inflammation? What are the mechanisms controlling AIBP expression and secretion? Transiently expressed AIBP is localized in the mitochondria of COS7 cells [18]; what is the subcellular localization of endogenous AIBP and its effect on mitochondrial function? The answers to these and other questions will define a novel regulatory circuitry for AIBP-regulated biological processes and provide new therapeutic avenues for inflammatory and angiogenic diseases.

Acknowledgments

Financial Support

Work in authors' laboratories is supported by NIH grants HL114734, HL132155, and U01 HL099997 and AHA grant 16BGIA27790081 to L.F., and NIH grants NS102432, HL135737, HL136275 and NS104769 to Y.I.M.

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Figure 1.

A, AIBP-mediated cholesterol efflux in regulation of Notch signaling. AIBP-mediated cholesterol efflux disrupts lipid rafts, which results in co-distribution of Notch1 with γ -secretase in non-raft domains, thereby facilitating Notch cleavage and signaling. **B, AIBP-mediated cholesterol efflux from ECs disrupts lipid rafts and inhibits VEGFR2 signaling.** VEGFA-triggered signaling requires VEGFR2 dimerization, which occurs in cholesterol-rich lipid rafts. AIBP-mediated cholesterol removal from the EC plasma

membrane disrupts lipid rafts, resulting in inhibited VEGFR2 signaling and restricted angiogenesis.

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Figure 2. AIBP impedes TLR4-mediated inflammatory signaling in myeloid cells. TLR4 dimerization is essential for innate inflammatory response. AIBP binds TLR4, enabling targeted cholesterol efflux, which disrupts TLR4 dimerization and represses TLR4 signaling. This AIBP-mediated effect results in inhibited inflammatory responses.