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AIBP, NAXE and Angiogenesis: What's in a Name?

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The article by Mao et al. shows that apolipoprotein A-I binding protein (AIBP) limits angiogenesis through regulation of Notch 1 signaling.[1] Deletion of AIBP increased vascular density and improved perfusion in a murine ischemia model. AIBP expression was increased in patients with ischemic cardiomyopathy. In an independent study this protein, renamed NAXE, has been shown to participate in recovering S-tetrahydro-nicotinamide adenine dinucleotide (S-NADHX) by epimerizing R-NADHX. So the question becomes how does an enzyme that participates in metabolite repair by recovering reducing intracellular equivalents participate in angiogenesis?

AIBP has been reported to avidly bind apoA-I, the principal protein component of high density lipoprotein (HDL). Loss of AIBP was found to accelerate angiogenesis without affecting the integrity of vessel walls. Using Apoa1bp$^{-/-}$ mice, the present paper has provided evidence that AIBP plays a role in angiogenesis that involves cholesterol metabolism and Notch signaling.[1] These studies suggest AIBP down regulates Notch 1 by a process that depends on γ-secretase activity. γ-Secretase is an intramembrane protease complex composed of four integral membrane proteins: APH1, Nicastrin, PEN2 and presenilin. Intramembrane proteolysis is highly conserved process for cell signaling. Presenilin cleaves only proteins that have a single transmembrane component with the C-terminus cytoplasmic and the N-terminus extracellular. The activation process is initiated by extracellular proteolysis empolying a sheddase. For example, ADAM metallopeptidase domain 17, removes the extracellular portion of the Notch1 receptor followed by intracellular presenilin proteolysis and release of the Notch1 intracellular domain (NICD). NICD signals through translocation to the nucleus or binding to other cytosolic proteins.[2, 3]

The current paper does not show a direct interaction between AIBP and the various proteins that regulate angiogenesis, e.g., Notch1, VEGFR2 or γ-secretase. However, treatment of human retinal microvascular endothelial cells (HRMECs) with HDL_3 plus AIBP showed significant translocation of Notch1 from raft fractions to non-raft fractions. Previous studies

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have suggested that γ-secretase was more active in releasing NICD when localized to non-raft regions of the membrane. Because raft regions are enriched in cholesterol, processes that remove cholesterol will reduce the fraction of membrane that exists as lipid rafts, e.g., incubating cells with methyl-β-cyclodextrin. When NICD release was studied in HRMECs AIBP or HDL_3 were not particularly active by themselves, but a combination of AIBP and HDL_3 was as effective as 10mM methyl-β-cyclodextrin in increasing NICD.

In other studies reported here the authors show that increased HDL levels can reduce angiogenesis. *Apoa1bp*$^{-/-}$ mice crossed with apoA-I transgenic mice had higher levels of HDL and did not display the proangiogenic phenotype seen in *Apoa1bp*$^{-/-}$ mice. Consistent with this observation they report that NICD levels were elevated and VEGFR2 phosphorylation reduced, a mechanistic indication that angiogenesis was inhibited.

However, there may be more to the mechanism of action of AIBP. The APOA1BP gene that codes AIBP was recently renamed NAXE by the HUGO Gene Nomenclature Committee. This protein has been well studied by several other groups. Functionally AIPB has been described as an epimerase that converts R-NADHX to biologically useful S-NADHX.[4] Recent studies have suggested that NAXE or AIBP participates in metabolite repair, one part of a set of dedicated systems employed by cells to rescue damaged metabolites.[5] In the absence of NAXE protein there is an increase in cyclic-NADHX that has been shown to inhibit cellular NADH dehydrogenases.[6–8] Two splice variants of AIBP are synthesized with the longer form predicted to reside in the mitochondria and the shorter form remaining in the cytosol.[7] As an indication of its importance mutations in the APOA1BP gene are associated with lethal neurometabolic disorders of childhood.[6, 9] There is controversy regarding whether AIBP is exclusively intracellular or secreted, with Ritter et al. (2002) demonstrating its presence in urine, cerebrospinal fluid, and in the serum of some septic patients, but not in the serum of healthy patients.[10] HepG2 cells were also reported to secrete small amounts of AIBP.[10]

Conclusion

The specific mechanism of action for the protein product from APOA1BP or NAXE needs to be clarified. At first glance the functions of AIBP described by different groups seem to be inconsistent with a unified mechanism of action that explains all of the experimental details. However, hypoxia is reported to promote angiogenesis and the hypoxic state may also be one in which there are insufficient levels of reducing agents due to changes in the redox state of the cell. More experimentation is needed to clarify the mechanism of AIBP as related to angiogenesis. A brief summary of what is known about AIBP is included in Table 1.

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Table 1

Summary of AIBP

Listing	Result
Gene Name	NAXE
Defined Protein Function	NADHX epimerase
Biochemical Outcomes	Regulates angiogenesis
Other Attributes	Redirects γ-secretase to non-raft regions of membrane
Diseases due to absence	Lethal Neurometabolic disorders of childhood