JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 3, 2017

ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2017.05.002

EDITORIAL COMMENT

# Lipoprotein(a)

## A Taxi for Autotaxin Takes a Toll in Calcific Aortic Valve Disease*

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Ectoenzymes play particularly important roles in the regulation of extracellular matrix mineralization. The prototypic example is evident in bone alkaline phosphatase (i.e., the bone/liver/kidney alkaline phosphatase [TNAP]) (1,2). This lipid-tailed enzyme is associated with mineralizing matrix vesicles, hydrolyzing, and dephosphorylating key negative regulators of tissue mineralization, including pyrophosphate and phospho-osteopontin (3), respectively. Genetic deficiency in TNAP results in hypophosphatasia, a variably severe bone disorder characterized by skeletal weakening due to reduced mineralization (1,2). Human molecular genetics has also provided insights into other types of tissue mineralization, including arterial calcification. The generalized arterial calcification of infancy is due to deficiency in ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) family member 1 (4), another ectozyme necessary for the generation of pyrophosphate (discussed earlier) and adenylate, a precursor to adenosine. A third ectoenzyme, called CD73/NT5E, is responsible for metabolizing extracellular adenylate to adenosine (5). Once again, deficiency in the CD73 ectoenzyme causes severe peripheral arterial calcification but confined to the lower extremity, mediated in part via dysregulated TNAP up-regulation.

A fourth ectoenzyme, ENPP family member 2 (ENPP2), also known as autotaxin, has recently emerged as important in the context of calcific aortic valve disease (CAVD) (6). Autotaxin possesses a phospholipase D activity that is required for enabling its preferred lysophospholipid substrate (lysophosphatidylcholine) to direct the osteogenic differentiation of valve interstitial cells via the enzymatic product lysophosphatidic acid (LysoPA). LysoPA-activated pro-inflammatory receptors upregulate paracrine bone morphogenetic protein 2 cues—a powerful morphogen signal that then directly activates the osteogenic program. However, the pathobiological consequences of the physical interactions been autotaxin and lipoprotein (a) (Lp[a]), a well-defined risk factor for CAVD (7), have only recently emerged (6,8). Lp(a) directly binds to ENPP2/autotaxin (6). As such, Lp(a) immediately juxtaposes ENPP2/autotaxin enzyme activity to oxidized choline phospholipids, including those lysophosphatidylcholine substrates that yield osteogenic LysoPA signals. Of note, deficiency in the type I LysoPA receptor *Lpar1* results in global reduction in osteogenesis and bone mass (9). The sources of ENPP2/autotaxin are diverse; although valve interstitial cells themselves can produce autotaxin (6), the adipocyte (10) and hepatocyte (10,11) are also key sources as potentially relevant to CAVD risk (12,13).

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In this issue of *JACC: Basic to Translational Science*, Torzewski et al. (14) confirm and extend these emerging data by examining the relationship between autotaxin/ENPP2 and valve LysoPA levels in human CAVD

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

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The author attests he is in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

specimens with increasing degrees of disease severity. They showed that the C16:0- and C18:1-LysoPA species are convincingly enriched in subjects with transaortic valve gradients. Immunohistochemical staining confirmed significantly increased accumulation of Lp(a), ENPP2/autotaxin, and oxidized phospholipids in valves with advancing histopathological grade. A chemiluminescent enzyme-linked immunosorbent assay for autotaxin-apolipoprotein(a) (apo[a]) and autotaxin-apolipoprotein B confirmed measurable circulating levels of this pro-osteogenic particle (6) in patients with CAVD; however, levels were not related to the extent or progression of disease. Thus, the recruitment of ENPP2/autoxin and its substrates to sites of cardiovascular lipoprotein accumulation, as directed by Lp(a), enables an osteogenic milieu for interstitial cells capable of initiating and organizing valve mineralization.

Given the convergence of recent data, how might one best stitch these observations together to further its translation? Without a doubt, the development of assays capable of quantifying circulating autotaxin complexes with apo(a)/apolipoprotein B is enabling and might help portend risk for clinical progression of CAVD. Indeed, Nsaibia et al. (8) have provided intriguing evidence supporting this notion; autotaxin-Lp(a) complexes are associated with the risk for CAVD in patients with coronary artery disease. Identifying those at greatest risk for progression from valve sclerosis to CAVD is a major unmet need (15); should plasma autotaxin-Lp(a) complex levels add to the value of assessing aortic valve calcium (16,17), this would be a major advancement. However, most excitingly, these data add to the evidence indicating that targeting autotaxin/ENPP2 activity might represent a therapeutic strategy to inhibit the progression of CAVD (18). Although ENPP2/autotaxin-null mice are embryonic lethal due to impaired vascular stabilization (19), global conditional deletion in the adult mouse has no overt effect on mortality, indicating that pharmacological inhibition with an acceptable therapeutic window is feasible (20). The new autotaxin-apo(a) enzyme-linked immunosorbent assay introduced (14) may offer a potential biomarker to identify those with greatest potential to benefit from ENPP2/autotaxin-based therapies (18).

Overall, our understanding of the molecular pathogenesis of CAVD is rapidly advancing and offers novel therapeutic strategies to improve the health and outcomes of these patients with CAVD.

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**KEY WORDS** calcific aortic valve disease, ectoenzymes