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The endothelial-metabolic axis: a novel cardiometabolic disease target

Jason C Kovacic, MD, PhD¹

¹The Zena and Michael A. Wiener Cardiovascular Institute and Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, New York, NY

Abstract

Endothelial to mesenchymal transition (EndMT) involves cellular phenotypic switching from an endothelial to mesenchymal state. Interest in EndMT has been heating up with the appreciation that it plays an important role in several cardiovascular diseases. New evidence indicates that fatty acid oxidation and cell metabolism are major factors controlling this process.

Keywords

endothelial to mesenchymal transition; EndMT; endothelial; metabolic; fatty acid oxidation; cardiovascular

The scientific field of cellular transition is expanding at a very fast pace indeed. As a comment that I will revisit later, the recent paper and the focus of this Spotlight article, “A Metabolic Basis for Endothelial to Mesenchymal Transition” by Xiong et al (1), is yet another major addition to the literature and body of knowledge regarding this process. With this manuscript, Xiong et al (1) have made a significant contribution and effectively opened an entirely new area of research – being that the process of endothelial to mesenchymal transition (EndMT) is regulated by fatty acid oxidation (FAO). Moreover, FAO and metabolic factors appear to be intimately involved with EndMT at multiple levels, and conversely, cells undergoing EndMT exhibit an altered metabolic status. But more of this later. First, how did we get to this point of a veritable explosion of interest in cell transition; what is it, and why all the fuss?

Interest in cell transition began over 5 decades ago with pioneering research showing that epithelial cells in the developing chick can transition in phenotype to become embryonic mesoderm (2, 3). After some debate, the process was ultimately named epithelial to mesenchymal transition (EMT). In brief, EMT involves a phenotypic switch from regularly arranged epithelial cells that are aligned along a basement membrane with classic features of

Address for correspondence: Jason Kovacic, Icahn School of Medicine at Mount Sinai, Cardiology Department, One Gustave L. Levy Place, Box 1030, New York, NY, 10029, Jason.kovacic@mountsinai.org, Website: <http://labs.icahn.mssm.edu/kovaciclab/>.

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apico-basal cell polarity and abundant expression of intercellular adhesion molecules, to mesenchymal cells that exhibit features such as loss of cell polarity and cell-cell adhesion, increased migratory capacity, and increased mesenchymal protein and gene expression (4). Classic mesenchymal cell types include mesodermal cells, fibroblasts, smooth muscle cells, osteocytes, chondrocytes and adipocytes (Figure).

While *epithelial* to mesenchymal transition has been widely explored and is known to be of importance in development, malignancy and adult tissue fibrosis, studies of *endothelial* to mesenchymal transition have been slower to emerge. Because the endothelium is a subtype of epithelium, EndMT can be considered as a subtype of EMT. While reports from the mid 1970's suggested a role for EndMT during cardiovascular development (5), it was only as recently as 2007 that the first report emerged which implicated EndMT in adult cardiovascular disease – in this case being that endothelial cells can undergo EndMT and participate in cardiac fibrosis (6). Since that time, interest in EndMT has grown exponentially. For example, among many studies, endothelial cells were recently shown to transition to fibroblast-like cells and migrate into atherosclerotic plaques where they are associated with the degree of plaque instability and rupture (7). Other adult cardiovascular diseases/states where a role for EndMT has now been suggested include pulmonary hypertension, vein graft remodeling, and in cardiac valve pathology (4).

Given this seemingly pervasive presence across a spectrum of adult cardiovascular diseases, it is unsurprising that intense efforts have recently been invested to unravel and understand EndMT. Until now, common wisdom was that it was primarily under the control of the TGF- β pathway – which includes the rich panoply of up- and down-stream members of the TGF- β signaling cascade (Figure). Beyond the TGF- β superfamily, other reported mediators of EndMT included certain Interleukins and FGFs, Wnt/ β -catenin signaling and oxidative stress. However, it is widely agreed that a vast amount remains to be discovered and understood about EndMT. It is in this context that the paper “A Metabolic Basis for Endothelial to Mesenchymal Transition” was published from the laboratory of Toren Finkel (1).

In this study, the authors undertook a thorough exploration of the role of cellular metabolism in EndMT (1). As a starting point, they leveraged standard *in vitro* EndMT models based on TGF- β + Interleukin-1 β stimulation, and immediately identified that EndMT is associated with an increase in certain short chain acylcarnitines, reduced endothelial FAO, and an early decrease in carnitine palmitoyltransferase 1A (CPT1A) levels - an enzyme that plays an obligate role in FAO. Accordingly, overexpression of *CPT1A* effectively blocked the induction of EndMT, while *CPT1A* knockdown induced EndMT *in vitro* in the absence of TGF- β or Interleukin-1 β . Although *CPT2* levels were unchanged with EndMT, knockdown of *CPT2* induced EndMT in a similar fashion to *CPT1A* knockdown. To further dissect these pathways, Xiong et al (1) then demonstrated that EndMT was also associated with a reduction in acetyl-CoA levels, and that an increase in cytosolic acetyl-CoA suppresses TGF- β -induced EndMT, while a reduction in cytosolic acetyl-CoA levels activates EndMT. In addition, acetyl-CoA was found to regulate EndMT by altering SMAD7 protein levels. *In vivo* using transgenic mice with endothelial-specific knockout of *CPT2* Xiong et al (1) were able to validate many of their *in vitro* findings. Notably, they were able to show that

endothelial-specific *CPT2* knockout led to increased EndMT with pathological thickening of the mitral valve *in vivo* (the mitral valve is known to partially arise via EndMT during cardiac development). In summary, Xiong et al (1) demonstrated that endothelial FAO and TGF- β signaling are closely intertwined, and that they act in concert to control endothelial cell fate and EndMT. This study is a significant advance on prior EndMT knowledge, and opens the door to targeting of FAO to impact any number of the growing list of diseases where EndMT likely plays a pathologic role.

This evolution of our understanding that FAO and cellular metabolism regulate EndMT, as well as prior knowledge of other influences of metabolic factors on the endothelium (e.g., obesity is associated with endothelial dysfunction (8)), begs one final question. Does this control also operate in the reverse direction? That is, can the endothelium regulate metabolism? Of relevance, well described endothelial roles include metabolically relevant tasks such as controlling angiogenesis, nutrient passage and vasomotor tone. Accordingly, a small but growing body of literature has clearly documented this to be the case, and that the endothelium may indeed exert profound influence on thermoregulation, obesity, adipose type (i.e. white versus brown), fatty liver, insulin sensitivity and global systemic metabolic status (9). Moreover, endothelial-specific targeting of key genes such as vascular endothelial growth factor receptor-1 (VEGFR1) was recently proposed as a novel strategy for the treatment of obesity and diabetes (9).

In conclusion, we appear to be glimpsing just the proverbial ‘tip of the iceberg’ in terms of the seemingly profound and bi-directional inter-relations between the endothelium and metabolism at both the local and systemic levels. With the endothelium being arguably one of the largest organs in the body, and with the current global epidemic of obesity and related cardiometabolic diseases, the endothelial-metabolic axis promises to be a hot area of research for the coming years.

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Figure. EndMT and its key signaling pathways

At the top is shown typical endothelial cells with underlying basement membrane. With EndMT, endothelial cells undergo a series of fundamental phenotypic changes and acquire a mesenchymal cell phenotype (bottom). Figure produced using Servier medical art.