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CELLULAR AND MOLECULAR
GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Making the Best of a Competition: the CREB3L3–SREBP Axis in Arteriosclerosis

Obesity is a serious global health burden, with more than 2 billion people being overweight, of whom approximately one-third suffer from obesity.[1,2] Abdominal obesity is linked to various cardiovascular and metabolic disorders, including arteriosclerosis, which is a leading cause of mortality and morbidity worldwide.[3] Arteriosclerosis is controlled directly by lipid metabolism, which is orchestrated by a network of transcription factors.[4–6]

The cyclic AMP-responsive element-binding protein 3 like 3 (CREB3L3) is a membrane-bound transcription factor that is expressed exclusively in the liver and intestine and controls multiple metabolic functions, including glucose and lipid metabolism and cholesterol absorption.[7–9] The metabolic consequences of CREB3L3 gene ablation or overexpression have been studied extensively in the past decade.[5,9–11] Whereas CREB3L3 deficiency leads to massive accumulation of hepatic lipids and to an increase in plasma triglyceride (TG) levels, its overexpression reduces plasma TG levels by promoting the hepatic expression of regulators of arteriosclerosis, such as apolipoprotein A4 (Apoa4), Apoa5, and Apoc2.[10,12–14] Loss of CREB3L3 in a common mouse model of arteriosclerosis (low density lipoprotein receptor [$LDLR^{-/-}$] mice) increases the frequency of arteriosclerotic lesions, indicating a critical contribution of CREB3L3 to arteriosclerosis.[13] Although much has been learned about the physiological functions of CREB3L3, the action of CREB3L3 at the hepatic and intestinal levels is still an emerging area of research, as is that on CREB3L3-interacting partners.

The study by Nakagawa et al[15] in this issue of *Cellular and Molecular Gastroenterology Hepatology* sheds additional light on the emerging role of CREB3L3 in arteriosclerosis. Using elegant murine models with liver- and intestine-specific CREB3L3 null mutations, Nakagawa et al[15] remarkably showed that both liver- and intestine-specific CREB3L3 deficiency additively promoted arteriosclerosis. Moreover, the overexpression of CREB3L3 suppressed the formation of arteriosclerotic lesions in $LDLR^{-/-}$ mice. They showed that CREB3L3 regulates arteriosclerosis by promoting the activation of antiatherogenic fibroblast growth factor (FGF)21 and APOA4, and inhibiting sterol regulatory element-binding proteins (SREBPs), key transcriptional regulators of cholesterol and lipid metabolism.[16] Although the control of FGF21 and APOA4 expression by CREB3L3 was expected,[5,12,14] the characterization of the molecular competition between SREBP and CREB3L3 is novel to the current work.

Mechanistically, Nakagawa et al[15] found that the antagonism between CREB3L3 and SREBP occurs during trafficking from the endoplasmic reticulum (ER) to the Golgi apparatus (Figure 1). CREB3L3 and SREBP are activated through the same process of regulated intramembrane proteolysis, and both need to be cleaved in the Golgi apparatus.[7] CREB3L3 competes with SREBPs for cleavage in the Golgi by promoting the formation of a CREB3L3/*INSIG1*/SREBP cleavage-activating protein/SREBP complex, which causes ER retention of SREBP proteins (Figure 1). Conversely, in the CREB3L3-deficient liver, SREBP-1 and SREBP-2 activity were increased and promoted TG and cholesterol synthesis. In the normal liver, CREB3L3 is up-regulated during fasting and down-regulated under feeding conditions; SREBP is regulated in a reciprocal manner. Thus, in healthy nutritional states the 2 factors do not encounter each other in the ER. However, in metabolic disturbances with high atherogenic risk, these 2 proteins are expressed concurrently and CREB3L3 can inhibit SREBP function.

The results of this study fit well with previous work showing that hepatic and intestinal CREB3L3 contribute to cholesterol metabolism.[10,11,13] Consistent with a previous report that CREB3L3 controls liver X receptor signaling,[17] Nakagawa et al[15] also confirmed decreased liver X receptor signaling and an increased lipid content in the intestines of $LDLR^{-/-}$ $CREB3L3^{-/-}$ mice. However, in contrast to previously published findings showing that the atherogenic phenotype of CREB3L3 mice is dependent on plasma FGF21,[5,11,18] in the current study the deficiency of *FGF21* in $LDLR^{-/-}$ Tg CREB3L3 mice did not negate the amelioration of arteriosclerosis, suggesting that FGF21 is not the sole contributor to the anti-arteriosclerosis effects of CREB3L3.

There were a few limitations to this study. First, the observations were based solely on murine models and in vitro cell culture assays. Because there is a difference in lipid metabolism between rodents and human beings, the pathophysiological relevance of these findings needs to be confirmed in future clinical studies. Second, multiple non-synonymous mutations in CREB3L3 that produce a hypomorphic or nonfunctional Creb3L3 protein were identified in patients with extreme hypertriglyceridemia[14,19]; it remains to be analyzed how these mutations affect the antagonism of CREB3L3 by SREBP. Other important aspects that also remain to be characterized are the binding domains for the interaction of SREBP and CREB3L3, as well as other novel interacting partners of the CREB3L3–SREBP complex.

In summary, Nakagawa et al[15] have enhanced our understanding of the complex regulation of lipid metabolism, showing a functional competition between CREB3L3 and SREBP and its consequences to the progress of arteriosclerosis. Therapeutic strategies designed to modulate CREB3L3

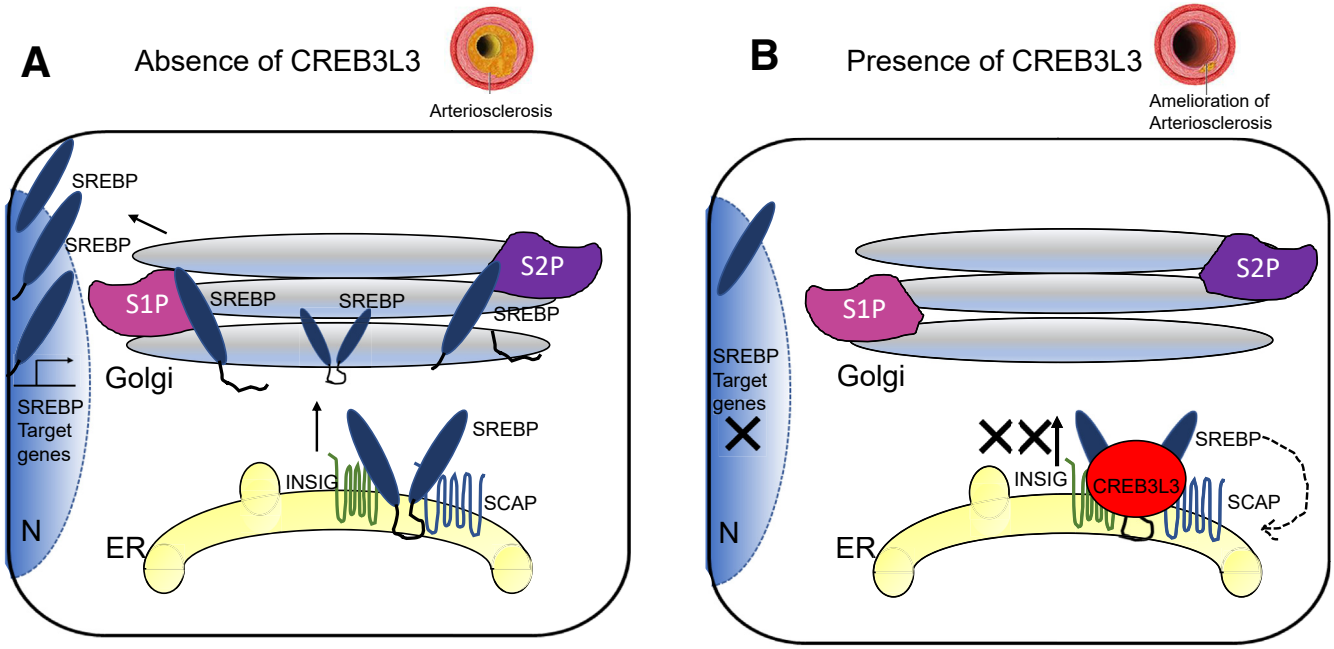

Figure 1. The functional competition between CREB3L3 and SREBP in arteriosclerosis. Schematic diagram showing the competitive antagonism between CREB3L3 and SREBP in arteriosclerosis. (*A*) CREB3L3 deficiency leads to increased ER to Golgi trafficking of SREBPs and translocation of SREBP to the nucleus, resulting in activation of SREBP target genes and arteriosclerosis. (*B*) When present, CREB3L3 prevents the ER to Golgi trafficking of SREBPs, thus inhibiting nuclear translocation of SREBPs, and reduced activation of SREBP target genes, which ameliorates arteriosclerosis phenotypes. INSIG, Insulin induced gene 1 protein; SCAP, Sterol regulatory element-binding protein cleavage-activating protein.

and/or SREBP cleavage, trafficking, or subcellular localization might be beneficial in the treatment of hyperlipidemia, arteriosclerosis, and obesity-associated metabolic diseases.

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Conflicts of interest
The author discloses no conflicts.


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2352-345X
https://doi.org/10.1016/j.jcmgh.2021.01.002