

# TGF- $\beta$ ENHANCERS TARGETING CANONICAL SIGNALLING ARE A NOVEL CLASS OF ANTI-INFLAMMATORY AGENTS FOR PREVENTING AND TREATING ASCVD

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For the last several decades, cholesterol has been thought to cause atherosclerotic cardiovascular disease (ASCVD). Limiting dietary cholesterol intake has been recommended to reduce the risk of the disease. However, several recent epidemiological studies do not support a relationship between dietary cholesterol and/or blood cholesterol and ASCVD. The role of cholesterol in ASCVD is now uncertain. Accumulating evidence indicates that TGF- $\beta$ , an anti-inflammatory cytokine in the circulation, protects against ASCVD and that suppression of canonical TGF- $\beta$  signaling (Smad2-dependent) is involved in the development of ASCVD. Recently, we demonstrated that 7-dehydrocholesterol (7-DHC; an immediate biosynthetic precursor of cholesterol), but not cholesterol, suppresses canonical TGF- $\beta$  signalling in target cells/tissues and causes ASCVD in vivo. We have identified TGF- $\beta$  enhancers which are therapeutic agents for ASCVD in human patients and animal models. They counteract the 7-DHC mediated suppression of TGF- $\beta$  canonical signalling in aortic endothelium. TGF- $\beta$  enhancers can be classified into 4 types: Type I TGF- $\beta$  enhancers: cholesterol biosynthesis inhibitors (e.g. statins); Type II TGF- $\beta$  enhancers: 7-DHC extruding compounds which include triterpenoids (e.g. betulinic acid), polyphenols (e.g. cyanidin), antioxidants (e.g. vitamin E) and ethanol; Type III TGF- $\beta$  enhancers: endocytosis inhibitors (e.g. dynasore). These agents enhance TGF- $\beta$  signalling by sustaining TGF- $\beta$  receptor signalling at the plasma membrane and Type IV TGF- $\beta$  enhancers: fusogenic compounds such as DMSO, ethanol and resveratrol. Since, these four types of TGF- $\beta$  enhancers utilize different mechanisms to enhance such signalling, combinations of these types of TGF- $\beta$  enhancers with additive and/or synergistic effects may lead to strategies to treat and/or prevent ASCVD.

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