Endothelial Nogo-B Regulates Sphingolipid Biosynthesis to Promote the Onset of Pathological Hypertrophy During Chronic Pressure Overload

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Chronic pressure overload leads to an initial compensatory cardiac hypertrophy, and eventually to heart failure. The mechanisms regulating the transition from adaptive to pathological cardiac hypertrophy remain elusive. We recently discovered that endothelial Nogo-B, a membrane protein of the ER, regulates vascular functions by inhibiting the rate-limiting enzyme in *de novo* sphingolipid biosynthesis, serine palmitoyltransferase (SPT). Here, we show that sphingolipids produced by the vasculature, particularly S1P, protect the heart function during pressure overload, through a paracrine mode of action. SPT activity is upregulated in banded hearts *in vivo*, as well as in TNF-α-activated endothelium *in vitro*, and loss of Nogo-mediated brake on SPT increases the production of S1P, which enhances the coronary vasculature compliance to high pressure and endothelial barrier. Hence, mice lacking Nogo-B, systemically or specifically in the endothelium, are resistant to the onset of pathological hypertrophy. Furthermore, pharmacological inhibition of SPT with myriocin restores permeability, inflammation, and heart dysfunction in Nogo-A/B-deficient mice to wild-type levels; whereas SEW2871, an $S1P_1$ receptor agonist, prevents myocardial inflammation and dysfunction in WT banded mice. Our study identifies a critical role of endothelial sphingolipid biosynthesis and its regulation by Nogo-B in the development of pathological cardiac hypertrophy, and proposes a potential new therapeutic target for the attenuation or reversal of this clinical condition.

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