ENPP1-Fc inhibits proliferation of vascular smooth muscle cells

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Vascular Smooth Muscle Cell (VSMCs) proliferation-associated stenosis is a major hallmark in the pathogenesis of Generalized Arterial Calcification of Infancy (GACI), an ultra-rare disease associated with ENPP1 loss of function mutations in the majority of patients. ENPP1 is an ectonucleotide pyrophosphatase that hydrolyzes ATP and serves as a key regulator of bone mineralization; however, the role that ENPP1 plays in intimal proliferation is poorly understood. Knockout mice lacking ENPP1 do not recapitulate the phenotype of intimal thickening, a common pathological feature in most GACI patients. Here, we examined the impact of ENPP1 on proliferation of primary rat VSMCs. Silencing ENPP1 using siRNA led to a significant increase in proliferation of VSMCs relative to that of cells transfected with negative control siRNA. This increased proliferation was inhibited by over expression of ENPP1 using an adenoviral vector encoding mouse ENPP1cDNA. Treatment of VSMCs with the ENPP1- reaction products AMP or adenosine resulted in moderate inhibition of VSMC proliferation, while treatment with the ENPP1-Fc fusion protein inhibited VSMC proliferation significantly. In contrast, neither addition of bisphosphonates, a current off-label treatment used for GACI, nor inorganic pyrophosphate (PPi) affected proliferation of VSMCs. In summary, using both loss of function and gain of function approaches, we demonstrated that ENPP1 negatively regulates VSMC proliferation, and that ENPP1-Fc protein replacement is effective in inhibiting proliferation associated with loss of ENPP1 in VSMCs. These findings suggest that ENPP1 enzyme replacement may serve as a potential therapeutic approach for treating myointimal proliferation in GACI disease.

Biography

Yan Yan has completed her PhD at Tokyo Medical and Dental University and Post-doctoral studies from Beth Israel Deaconess Medical Center and Wayne State University School of Medicine. She is a Principal Scientist (Research Scientist IV) in Alexion Pharmaceuticals and has obtained 9 patents and published approximately 18 peer-reviewed scientific manuscripts.

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