The Contribution of Cellular Mechanical Oscillation in Vascular Smooth Muscle Cell Migration

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Introduction: Aberrant cell proliferation and migration are key contributors to the development of various diseases, including atherosclerosis, restenosis in vascular tissue engineering, and cancer metastasis. During cell migration, the cytoskeleton undergoes dynamic assembly and disassembly to extend the cell membrane forward and explore its surroundings. Our studies suggest that cell migration correlates with cellular mechanical oscillations rather than static cell mechanics. Thus, we propose that regulating cell migration by targeting cellular mechanical oscillations is a promising strategy for treating and preventing cell migration-related diseases such as cardiovascular diseases (CVD).

Materials and methods: Vascular smooth muscle cells (VSMCs) were isolated from the descending thoracic aorta of male ApoE$^{-/-}$ and male WT mice. We used an Atomic Force Microscope (AFM) (MFP-3D-BIO, Asylum Research, Santa Barbara, CA) to study the oscillation in VSMC mechanics. Additionally, live VSMC submembranous cytoskeleton architecture was examined using AFM and confocal microscopy (IX83 FV1200, Olympus, USA). We analyzed the real-time data of cellular mechanics and cytoskeleton architecture using a data-driven mathematical model developed in our lab. For all experiments, we used two-way ANOVA to infer statistical significance.

Results and Discussion: We found that ApoE$^{-/-}$ VSMCs had a significantly higher E-modulus compared to WT VSMCs (Figure 1). The increased stiffness of ApoE$^{-/-}$ VSMCs was associated with a greater degree of stress fiber alignment, as evidenced by AFM-generated force maps and stress fiber topography images. Furthermore, ApoE$^{-/-}$ VSMCs exhibited a significantly higher mechanical oscillation amplitude compared to WT cells. This result can be explained by the difference in cholesterol loading between ApoE$^{-/-}$ and WT cells after animal exposure to a high-fat diet, which leads to altered VSMC adhesion and enhanced cell migration, as we previously demonstrated in our study [1].

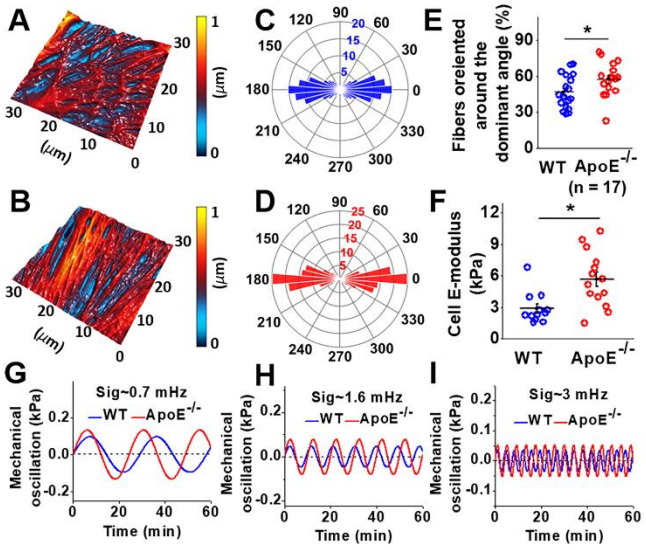

Fig. 1. Submembranous cytoskeletal orientation and cell E-modulus. Representative AFM images of submembranous cytoskeleton for VSMCs isolated from WT (A) and ApoE-/- mice (B). Polar histogram for cytoskeletal organization along the dominant fiber angle for WT (C) and ApoE-/- VSMCs (D). The quantified percentage of fibers orientated around dominant fiber angle (n=17) (E). Average cell E-Modulus during the real-time measurements (F). Three oscillatory signals (G-I) were detected in real-time VSMC mechanics. Compared to WT, ApoE-/- mice exhibited significant increases in cytoskeletal organization, cell E-modulus, and mechanical oscillation amplitude. (n =11 for WT, n =14 for ApoE-/-) ($p < 0.05$ for panels E&F).

Conclusion: The insights gained from this study on the mechanism of cellular dynamics and their link with cell migration in CVD will provide a basis for developing a novel therapeutic strategy to treat atherosclerosis by regulating the cell dynamics during VSMC migration and disrupting their contribution to disease development.

[1] H.J. Sanyour, N. Li, A.P. Rickel, H.M. Torres, R.H. Anderson, M.R. Miles, J.D. Childs, K.R. Francis, J. Tao, Z. Hong, Statin-mediated cholesterol depletion exerts coordinated effects on the alterations in rat vascular smooth muscle cell biomechanics and migration, The Journal of physiology 598(8) (2020) 1505-1522.