MULTISCALE COMPUTATIONAL MODELING OF NOTCH SIGNALING IN MECHANO-REGULATED GROWTH AND REMODELING

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Introduction

Arteries grow and remodel in response to mechanical cues. Hypertension, for example, is known to result in arterial thickening, but the underlying cellular mechanisms remain largely unclear. Notch signaling between vascular smooth muscle cells (VSMCs) plays important roles in arterial growth and remodeling (G&R) [1] and is affected by strain [2]. This suggests that Notch may be a key player in mechano-regulated G&R. Here, we investigated the role of Notch in hypertension using multiscale computational modeling.

Methods

A Notch signaling model [2] was adopted, simulating interactions between VSMC-bound Notch receptors and ligands, accounting for their sensitivity to strain. This model was coupled to a Finite Element (FE) model of arterial mechanics, including pre-stretches, to capture the influence of hypertension on VSMC phenotype, as modulated by Notch (Fig. 1A). In a subsequent study, the Notch model was coupled to a constrained mixture model [3], which considers the turnover and mechanics of arterial constituents, to capture in more detail the effects of Notch on VSMC behavior and associated tissue G&R in hypertension (Fig. 1B). This latter coupling was partly informed by *in vitro* data and also included a stress-driven stimulus for G&R to account for mechanisms other than Notch.

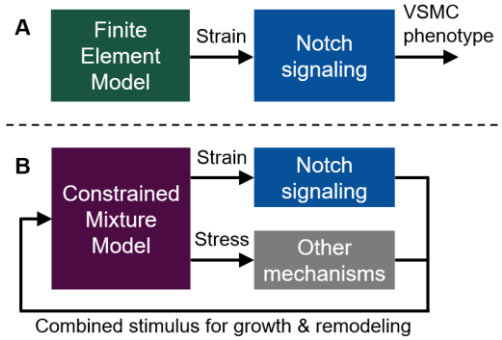

Figure 1. Schematic overview of the two multiscale computational models combining Notch signaling with tissue mechanics (A) and growth and remodeling (B).

Results

The results from the FE analysis show that the hypertension-induced increase in stretch, especially on the luminal side (Fig. 2A), resulted in a decrease in Notch activity, and thereby a shift of the VSMCs towards a synthetic phenotype with higher G&R activity (Fig. 2B). These predictions are consistent with experimentally observed thickening in hypertension [4]. The coupling of the Notch model to a constrained mixture model revealed that Notch regulates the arterial thickening (Fig. 2C) in hypertension predominantly by increasing VSMC proliferation (Fig. 2D). The artery was predicted to rely on other mechanisms to achieve full remodeling in terms of VSMC and collagen density (Figs. 2D & 2E), as observed *in vivo* [5] (Fig. 2, crosses).

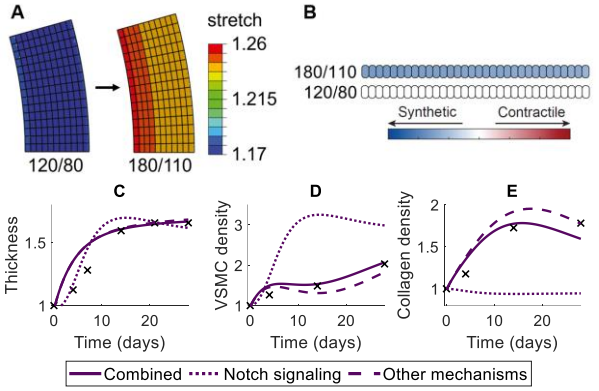

Figure 2. Predicted arterial stretch distribution (A) and phenotype of VSMCs (B) under normotension (120/80 mmHg) and hypertension (180/110 mmHg). Predicted time courses of arterial thickness (C) and normalized VSMC (D) and collagen (E) density in hypertension.

Discussion

Our simulations suggest that Notch mechanosensitivity may be a key mechanism in arterial G&R in response to hypertension. More knowledge on Notch may therefore be vital to increase our understanding of arterial adaptation. Notch may also play an important role in the search for novel therapies to steer G&R, for example in vascular disease or regeneration. Nevertheless, Notch alone cannot explain full remodeling, suggesting that it should be considered together with other pathways.

References

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