A Thermodynamic Framework to Investigate the Role of Cell Morphological Changes in Cerebral Aneurysm Growth

Ryan Coleman*[1] and Patrick Mcgarry[2]

[1]Biomedical Engineering, University of Galway – Ireland
[2]Biomedical Engineering, University of Galway – Ireland

Abstract

Aneurysmal tissue is pathologically weakened relative to healthy arterial vessels, highlighted by a decreased presence of elastin in cerebral arterial aneurysm tissue post-rupture, relative to healthy aortic vessels (1, 2). Throughout pathogenesis of cerebral aneurysms smooth muscle cells (SMCs) differentiate into synthetic "matrix remodelling" and proliferate phenotypes (3). Observations show thermodynamic fluctuations motivate cellular remodelling towards a homeostatic ensemble in similar contractile cells (4). We propose a novel thermodynamic framework to predict arterial remodelling based on the following processes: (i) initial elastin degradation; (ii) SMC morphological change; (iii) SMC differentiation into a proliferative synthetic state; (iv) synthesis of collagen ECM and growth of arterial tissue. In this framework, evolution in cell morphology and ECM synthesis is driven by a change in the free energy of the system from the homeostatic free energy associated with a healthy artery.
Our proposed mathematical framework incorporates the principle that an energetic stimulus, such as knock-out of elastin, causes free energy of the artery wall to diverge from homeostasis, resulting in cell and tissue remodelling. This results in a competition between cell-stretch and cell replication returning the system to a homeostatic state, with passive energetic requirements of stretch in collagen, elastin, and the passive matrix component. A constitutive law is proposed for active contractility observed in SMCs, predicting the concentration of stress fibres (SFs), dependent on cell stretch, found through thermodynamic equilibrium between chemical potentials of SFs with unbound cytoskeletal actin-myosin proteins (4). This thermodynamic equilibrium also effects the Gibbs free energy density of the cell, resulting in an energetic competition between SF formation and passive stretch of the cell cytoplasm and membrane. This framework is complimented by a constitutive law describing force balance conditions as well as energetic considerations in modelled arterial components of collagen, elastin, and the passive arterial matrix response (5).

Our model predicts that cells change their morphology in order to restore the Gibbs free energy of the artery wall to a homeostatic free energy. Significant deformation of the artery wall due to hypertension or elastin damage increases energetic demands for arterial vessel maintenance, which cannot be sufficiently restored to homeostasis through the mechanism of cell morphology change. This results in the differentiation of SMCs into a synthetic state. The synthetic state exhibits significantly reduced SF formation, such that its energetic contribution and contractile stress is reduced. However synthetic cells act to decrease free energy

*Speaker

of the system by replication of additional contractile SMCs, or increase free energy by causing passive tissue growth by deposition of arterial tissue, potentiating growth of the vessel circumference. We utilise this framework to predict fusiform aneurysm formation, and we compare predicted aneurysm growth rates of SMC and ECM morphological changes with clinical observations and histological images. This cell based thermodynamic framework represents a significant advance on previous phenomenological models of aneurysm growth that rely on stress- or strain-based growth algorithms.

References

(1) Robertson et al., ABME, 43:1502-1515, 2015.
(2) Nakagawa et al., JAHA, 7(17) 2018.
(3) Starke et al., Transl. Stroke Res., 5:338-346, 2013.
(4) Shishvan et al., BMMB, 17:1631-1662, 2018.
(5) Concannon et al., Acta. Biomater., 125: 154-171, 2021.
Acknowledgement: This research is funded through the EU Horizon Project GEMINI (Project no. 101136438).