A Novel Epigenetic Approach for Vascular Elastic Matrix Regeneration: Evaluating the Proteomic Interactions of siRNA-Based Gene Silencing in the EGFR Signaling Pathway of Abdominal Aortic Aneurysms

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Abdominal aortic aneurysms (AAAs) are a life-threatening condition with a ruptured mortality of 80-90% with no current drug-based therapies. They result from the thinning of media & adventitia in aortic walls due to the extracellular matrix (ECM) degradation caused by matrix metalloproteinase (MMP) overexpression. Elastic fibers are key components of the ECM involved in stretch, recoil, and healthy cell phenotypes maintenance, and do not naturally regenerate in proteolytic disorders (such as AAAs). This study investigated a novel gene silencing approach using small interfering RNA (siRNA) to assess regenerative outcomes in a proteolytic injury culture model of rat aneurysmal smooth muscle cells (EaRASMCs). It was hypothesized that inhibiting EGFR activity would be a useful therapeutic approach given that it stimulates one of the largest interlinked signaling networks (e.g. ERK & JNK) that may trigger downstream elastogenesis and anti-MMP effects. EaRASMCs were treated with varying concentrations of EGFR-targeting siRNA and the relative expression levels of 16 genes with possible associations with the EGFR pathway were gathered using real-time polymerase chain reaction. Based on these results, the optimal siRNA concentrations were further studied using Western blot and then immunofluorescence imaging to verify subsequent protein inhibition and visualize the expression of ECM proteins. Regenerative outcomes were successfully achieved through the upregulation of elastic matrix assembly and simultaneous inhibition of MMPs and ECM degrading proteins. The results of this modality demonstrate a mechanistic basis of a broader therapeutic approach to stimulate vascular tissue regeneration by reversing matrix pathophysiology to treat aneurysms prior to their fatal rupture.

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