ABSTRACT

Granzyme B (GzmB) is a serine protease that can be released into the extracellular spaces by immune cells during chronic inflammation where it is capable of degrading several components of the extracellular matrix (ECM). Apolipoprotein E (ApoE) is a protein highly expressed in the skin, where it can regulate inflammation through its anti-oxidative and anti-inflammatory properties. Mice deficient in ApoE develop an inflammatory skin phenotype when fed a high fat diet indicative of premature aging featuring ECM remodeling, hair graying, hair loss and frailty. I therefore hypothesized that GzmB contributes to skin aging, injury and impaired healing in ApoE knockout (ApoE-KO) mice through the degradation of ECM proteins. In the present dissertation, I identified the high fat diet-fed ApoE-KO mouse as a model that displays several characteristic features of skin aging including skin thinning and collagen disorganization. Further investigations also identified that high fat diet-fed ApoE-KO mice also show defects in cutaneous wound healing such as delayed wound closure, reduced contraction and altered collagen content. These changes became worse with age and high fat diet. To test the role of GzmB in this process, we generated GzmB/ApoE double knockout (DKO) mice. These DKO mice were protected from skin thinning and collagen disorganization even when fed a high fat diet, suggesting that GzmB is playing a role in ECM remodeling during aging in the skin of ApoE-KO mice. Further investigation revealed that GzmB-mediated decorin degradation was likely to be a key mechanism by which GzmB contributes to collagen disorganization and skin aging in ApoE-KO mice. Furthermore, DKO mice showed improved wound healing compared to ApoE-KO mice featuring faster wound closure, increased contraction and reduced fibronectin degradation. *In vitro* cleavage assays revealed that fibronectin fragments identified in non-healing ApoE-KO mouse wounds matched those generated by GzmB. In summary, my findings suggest that extracellular GzmB contributes to skin aging and impaired healing in ApoE-KO mouse skin through the degradation of ECM components such as decorin and fibronectin.