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Amplification of Intrinsic and Protective Ocular Surface Lipid Circuits as Novel Treatment Targets

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LAY ABSTRACT

It is now recognized that essential and frequent inflammatory and immune responses require counter-regulatory circuits that ensure their healthy resolution. The strategy of developing “resolution agonists” that amplify these intrinsic circuits is a new frontier in the battle against chronic inflammatory diseases. We have identified lipid circuits in the eye that drive healthy inflammatory/immune responses and wound healing. These protective lipid circuits are highly expressed in human/mouse corneas and mediate the protective actions of fish oils in the retina. Preliminary data demonstrates that females have a sex-specific inflammatory response, increased corneal injury and delayed wound healing. This estrogen-driven response correlates with reduced expression/activity of the protective lipid circuit in the cornea. Three specific aims will define the roles of this circuit in limiting Dry Eye induced disease in the cornea and lacrimal gland, and establish that its therapeutic amplification is an approach to treat and resolve Sjögren’s Syndrome pathogenesis.

SCIENTIFIC ABSTRACT

It is now recognized that controlled activation of leukocytes/lymphocytes, maintenances of selftolerance and inflammatory resolution depend on intrinsic protective circuits. The strategy of developing “resolution agonists” that amplify these circuits is a new frontier in the battle against chronic inflammatory diseases. We have identified ocular lipoxygenase (LOX)-driven lipid circuits that drive healthy inflammatory/reparative responses, nerve regeneration and control Tcell activation. This resolution circuit is highly expressed in human/mouse corneas and mediates the protective actions of docosahexaenoic acid in retinopathies. Preliminary data demonstrates that females have a sex-specific phenotype of inflammation, increased epithelial injury triggered by desiccating stress and delayed wound healing. This estrogen-driven phenotype correlates with reduced expression/activity of the 15-LOX/5-LOX-ALX receptor circuit. Three specific aims will define the roles of this circuit in limiting desiccating stress induced corneal and lacrimal gland pathogenesis, and establish that its therapeutic amplification is a valid approach to treat and resolve Sjögren’s Syndrome pathogenesis.