

Niral Gandhi, MD-Candidate
Baylor College of Medicine, Cullen Eye Institute
Houston, Texas

Activation of TGF- β on the ocular surface in dry eye
Recipient of 2010 Student Fellowship Award – SSF-CLAO ERF

Abstract

Specific Aims

Our project intends to address how TSP-1 deficient mice produce increased levels of IL-17a, when an accepted pathway of TGF- β activation from TSP-1 is not present or decreased in activity. We hypothesize that dry eye and desiccating stress increase bioactive TGF- β on the ocular surface that promotes a Th17 skewed immune response and that proteases other than TSP-1 activate latent TGF- β on the ocular surface.

Aim 1: We will initially evaluate and compare TGF- β expression and activation on the ocular surface and draining lymph nodes in wild-type and TSP-1 null mice.

Aim 2: To further elucidate the pathway, we will compare TGF- β expression and bioactivity in wild-type and TSP-1 null mice in response to experimental ocular surface desiccating stress.

Background

Recent work in the field has linked the absence of activity of the protein Thrombospondin-1 (TSP-1), a protein involved in the activation of TGF- β , to the development of lacrimal keratoconjunctivitis in mice. TSP-1 deficient mutants acquire a dry eye condition that is similar to Sjögren's syndrome. In fact, higher levels of IL-17a in splenocytes and the lacrimal glands have been noted in these mice compared to wild-type. These findings suggest there is an alternative mechanism for activating TGF- β on the ocular surface. Prior work in Dr. Pflugfelder's lab has focused on the efferent arm of the autoimmune cascade and the resulting damage to the ocular surface and has described 1) the upregulation of IL-17 on the corneal barrier secondary to desiccating stress and its subsequent damage to the corneal barrier and 2) the increase in levels and activity of MMP-3 and MMP-9 in dry eye disease.

Significance

The finding of a Th17 response in TSP-1 deficient mice implies a different mechanism of local activation of TGF- β produced by the ocular surface epithelium and by dendritic cells, crucial to the initiation of the Th17 skewed response. MMP activity has been shown to increase in response to dry eye and experimental desiccating stress. We, therefore, believe that MMPs, rather than Thrombospondin-1 are activating TGF- β on the ocular surface. In contrast, activation of TGF- β may be TSP-1 dependent in the draining lymph nodes. These studies would provide important information about the physiologic regulation of TGF- β activation on the ocular surface and the subsequent initiation of Th17 autoimmune responses.