Uveitis is a T cell-mediated inflammation of the eye, and it is the second leading cause of human blindness accounting for approximate 10% of cases of legal blindness in the United States. Hyperactivation of antigen-presenting cells (APCs) leading to an overactive T helper cell response is able to cause autoimmunity including experimental autoimmune uveoretinitis (EAU). The goal of our research is to understand how APCs become hyperactivated in uveitis. We have demonstrated that Tyro3, Axl and MerTK (TAM) family receptor tyrosine kinases are responsible for controlling APC activity. Triple knockout mice lacking all three TAM genes (tko mice) develop autoimmune disease in multiple organs including kidney, liver, lung, central nerve system and eye. These mice also, spontaneously produce retinal autoantigen-specific CD4+ T cells. Some of these T cells convert to resting, long-lived retinal autoantigen-specific memory T cells that render the tko mice more susceptible to retinal autoantigen stimulation. Immunization with retinal specific autoantigen, mimicking relapse in recurrent uveitis, such as Behcet’s, Ocular sarcoidosis and Vogt-Koyanagi-Harada diseases, elicits a dominant T helper-mediated inflammatory response in eye, which we link to hyperactivation of APCs and generation of antigen-specific memory T cells in tko mice. Mounting evidence suggests that TAM receptors play a negatively role in regulating APC activation, which in turn limit APC-mediated over activation of naïve T cell. The degree of initial T cell activation has been linked to conversion to autoantigen-specific memory T cells. Recruitment of these long-lived memory T cells is thought to be linked to relapse seen in uveitis and other autoimmune diseases. The researches in our laboratory aim to examine roles of TAM receptors in APC activation and subsequent the generation and recruitment of the memory T cells that cause disease relapses, and have a better understanding how the TAM deficient APCs affect generation, long-term persistence and reactivation of the retinal specific memory T cells in recurrent uveitis, so that the novel therapeutic targets will be discovered and new medication approaches will be proposed for prevention and cure of relapse-remission types of uveitis.

Grants:

R01-EY018830 (PI: Lu, Q), 09/30/2008-08/31/2013 6 calendar NIH/NEI $250,000.00 per year
Title: MerTK regulation of the PTTG and RPE phagocytosis

R01-Ey019891 (Co-PI with 10% effort, PI, Dr. Qiutang Li) 1.2 Calendar NIH/NEI 09/01/2010-08/31/2014 direct cost $250,000.00 per year
Title: Role of 14-3-3σ in development and repair of corneal epithelium

1R21EY021584-01 (Co-PI with 10% effort, PI: Qiutang Li), 0.72 calendar NIH/NEI 09/01/2011 – 08/31/2013 direct cost $275,000
Title: 14-3-3σ and epithelial differentiation in the eye and other tissues

Publications


Ye, F., Han, L., Lu, Q-J., Dong, W., Shao, H., Kaplan, JK., Li, Q., and Lu, Q. Retinal self-antigen induces a predominantly Th1 effector response in Axl and Merth double knockout mice. Journal of Immunology, 187:4178-4186, (2011). PMID:21918185; PMCID: PMC3190567


Huayi Lu, Qingxian Lu, Yajuan Zheng, and Qiutang Li. Notch signaling promotes the corneal epithelium wound healing. Molecular Vision 2012; 18:403-411. PMID:22355251; PMCID:PMC3285215