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Blockade of CD40/CD40L interactions early in life abolishes Sjögren's-like manifestations in aged NOD.H2^{H4} mice

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Primary Sjögren's syndrome (pSS) is an autoimmune disease that is characterized by autoantibodies (autoAbs). Longitudinal data demonstrate that pre-symptomatic autoAbs arise years to decades prior to the diagnosis of pSS. Understanding the underlying mechanisms and delineating if an early life window exists where autoAbs can be inhibited is critical for disease intervention. pSS is closely modeled in non-diabetic NOD.H2h4 mice where we detect autoAbs months before the neogenesis of salivary gland (SG) tertiary lymphoid structures and xerostomia. Importantly, shortly prior to the emergence of autoAbs, spontaneous splenic germinal centers (GC) appear early in life. To determine if SG ectopic follicles and autoAbs arise from spontaneous splenic GC early in life, GC's were disrupted by a single administration of anti-CD40L mAb at 4 weeks of age. Blockade of CD40/CD40L interaction effectively disrupted splenic GC for over 2 months. Moreover, loss of GC in the spleen was followed by a dramatic loss of SG ectopic follicle development in aged mice. Notably, a single administration of anti-CD40L at 4 weeks of age significantly inhibited autoAb titers. However, no effect on autoAb was observed if a single dose of anti-CD40L was given at 5 weeks of age. Our findings highlight the contribution of immune dysregulation to the development of organ-specific autoimmune disease. Furthermore, these data demonstrate that early prophylactic intervention can inhibit auto Abs and ectopic lymphoid structures in an animal model of pSS.

Biography

Tamer I Mahmoud joined MedImmune as a postdoctoral fellow in 2012. Working with the Autoimmunity group he is characterizing the events that initiate or exacerbate chronic inflammation in the salivary glands of a mouse model of primary Sjögren's Syndrome. Tamer's experience in autoimmunity is complemented by his long standing interest in studying the diversity of the B cell repertoire as well as cell subsets that respond to blood-borne pathogens. Tamer received his B.Sc. in Pharmaceutical Sciences from Cairo University. In 2009, he earned his PhD from the University of Alabama at Birmingham.

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