The use of mouse models to better understand mechanisms of autoimmunity and tolerance.

Abstract:

A major emphasis of our studies has been on developing a better understanding of how and why the skin serves as a target for immune reactions as well as how the skin evades becoming a target for destruction. For these studies we developed transgenic mice that express a membrane-tethered form of a model self antigen, chicken ovalbumin (mOVA), under the control of a keratin 14 (K14) promoter. K14-mOVA transgenic mice that express OVA mRNA and protein in the epithelia have been assessed for their immune responsiveness to OVA and are being used as targets for T cells obtained from OT-1 transgenic mice whose CD8+ T cells carry a V?2/V?5-transgenic T cell receptor with specificity for the OVA(257-264)-peptides (OVAp) in association with class I MHC antigens. Some of the K14-mOVA transgenic mice develop a graft-versus-host-like disease (GvHD) when the OT-1 cells are injected while others appear to be tolerant to the OT-1 cells. We found that ?c cytokines, especially IL-15, determine whether autoimmunity or tolerance ensues in K14-mOVA Tg mice. We also developed transgenic mice that express soluble OVA under the control of a K14 promoter (K14-sOVA) that die within 5-8 days after adoptive transfer of OT-1 cells and identified these mice as a model for more acute GvHD-like reactions. Spontaneous autoimmunity occurs when these K14-sOVA mice are crossed with the OT-I mice. In
contrast, we found that preventive or therapeutic OVAp injections induced a dose-dependent increase
in survival. In this review the characterization of 5 strains of K14-OVATg mice and underlying
mechanisms involved in autoimmune reactions in these Tg mice are discussed. We also describe a
strategy to break tolerance and describe how the autoimmunity can be obviated using OVAp. Finally,
a historical overview of using transgenic mice to assess the mechanisms of tolerance is also
provided.

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