Canine X-Linked Severe Combined Immunodeficiency

A Model for Investigating the Requirement for the Common Gamma Chain (γc) in Human Lymphocyte Development and Function

Abstract

Our laboratory has identified and characterized an X-linked severe combined immunodeficiency (XSCID) in dogs that is due to mutations in the common gamma (γc) subunit of the interleukin-2 (IL2), IL4, IL7, IL9, and IL15 receptors. Canine XSCID, unlike genetically engineered γc-deficient mice, has a clinical and immunologic phenotype virtually identical to human XSCID. It appears that species-specific differences exist in the role of the γc and its associated cytokines in mice compared to their role in humans and dogs, suggesting γc-deficient dogs may be a more relevant model for studying the role of the γc in humans. We are utilizing this model for a variety of studies to address:

1. Fundamental questions concerning the role of the γc in cytokine regulation and lymphocyte development.
2. The pathogenesis of XSCID.
5. Human hematopoietic stem cell development.

Introduction

Severe combined immunodeficiency (SCID) represents a heterogeneous group of genetic disorders characterized by the absence of T and B cell function, which usually results in death during infancy (1). In the past 10 yr, the genes responsible for most forms of SCID...
have been identified, cloned, and their function and expression characterized. The most common form of SCID is X-linked SCID (XSCID), which is due to mutations in the common gamma (γc) subunit of the receptors for interleukin-2 (IL2), IL4, IL7, IL9, and IL15 (2,3). Thus, the XSCID phenotype is the complex result of multiple cytokine defects. The shared usage of the γc by receptors for growth factors that are essential for normal B and T cell development and function explains the profound immunologic abnormalities and clinical severity of the disease.

XSCID boys present in the first year of life because of severe, recurrent, or persistent infections that generally begin between 3 and 6 mo of age, at a time when maternally derived antibody has virtually disappeared. The most striking clinical feature is a failure to thrive. The immunologic abnormalities have been recently reviewed (1,4–8). At the time of diagnosis, affected boys have markedly reduced or absent T cells that fail to proliferate in response to stimulation. Peripheral B cells are present in normal or increased numbers and have a virgin (IgM+) phenotype, but they fail to mature and function normally. The primary B cell defect is assumed to be the inability to class-switch from IgM to IgG, since bone marrow-transplanted XSCID boys who do not engraft donor B cells fail to produce IgG antibody following immunization with bacteriophage φX174 (7). Although a mutant γc has a profound effect on early human T cell differentiation, the observation that XSCID boys have normal or elevated numbers of IgM+ B cells and that peripheral IgM+ B cells from carrier females exhibit random X-chromosome inactivation (9) suggests that a mutant γc does not interfere with the early stages of human B cell development.

Since the discovery of the gene responsible for XSCID, γc-deficient mice have been created by homologous recombination (10,11). These mice appear to develop as well as their littermates. The thymus is hypoplastic, and the cellularity is approx 2–5% of normal. Interestingly, thymocyte differentiation does not appear to be arrested, since there is no significant alteration in the proportion of thymocyte subsets. Young γc-deficient mice lack peripheral T cells, but an age-related increase in the proportion and absolute numbers of splenic T cells has been reported (11). The peripheral T cells do not respond to mitogenic stimulation. In contrast to human XSCID patients, γc-deficient mice also have greatly diminished peripheral B cells due to a block in the expansion of pre-B cells in the bone marrow. Thus, there are immunologic differences between human XSCID patients and γc-deficient mice—a mutated γc appears to have a greater effect on T cell development in humans (10) and a greater effect on B cell development in mice (10,11). These findings suggest that species-specific differences may exist in regard to the role of γc-dependent cytokines and their receptors in the development and function of B cells and T cells in humans and mice.

The purpose of this article is to review another animal model of γc deficiency—canine X-linked severe combined immunodeficiency that was identified by our laboratory. Canine XSCID is a naturally occurring disease that results in a clinical and immunologic phenotype virtually identical to human XSCID and is due to mutations in the γc gene, making it a true homolog of the human disease (12–16). The mutation in our colony is a 4-bp deletion in the signal peptide region resulting in a frame-shift with a premature termination codon in exon 1. The predicted product is a truncated protein of 21 amino acid (aa) instead of the normal 373 aa, in essence representing a naturally occurring "knockout." A breeding colony of XSCID dogs was developed from a single carrier female resulting in all affected dogs having the same genetic defect.