

## Introduction

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## Mouse models of graft-versus-host disease\*

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 Published February 28, 2009.

### Introduction

Allogeneic hematopoietic cell transplantation (HCT) represents an important therapy for many hematological and some epithelial malignancies and for a spectrum of nonmalignant diseases (Appelbaum, 2001). The development of novel strategies such as donor leukocyte infusions (DLI), nonmyeloablative HCT and cord blood transplantation (CBT) have helped expand the indications for allogeneic HCT over the last several years, especially among older patients (Welniak et al., 2007). However, the major toxicity of allogeneic HCT, Graft-Versus-Host disease (GVHD), remains a lethal complication that limits its wider application (Ferrara and Reddy, 2005). Depending on when it occurs after HCT, GVHD can be either acute or chronic (Deeg, 2007; Weiden et al., 1979; Weiden et al., 1981; Lee, 2005). Acute GVHD is responsible for 15% to 40% of mortality and is the major cause of morbidity after allogeneic HCT, while chronic GVHD occurs in up to 50% of patients who survive three months after HCT. **Mouse models** have provided the majority of insights into the biology of this complex disease process.

The GVHD reaction was first noted when irradiated **mice** were infused with allogeneic marrow and spleen cells (van Bekkum and De Vries, 1967). Although **mice** recovered from radiation injury and marrow aplasia, they subsequently died with "secondary disease" (van Bekkum and De Vries, 1967), a syndrome that causes diarrhea, weight loss, skin changes, and liver abnormalities. This phenomenon was subsequently recognized as GVHD disease (GVHD). Three requirements for the developing of GVHD were formulated by Billingham (Billingham, 1966–1967). First, the graft must contain immunologically competent, now recognized as mature T cells. In both experimental and clinical allogeneic BMT, the severity of GVHD correlates with the number of transfused donor T cells (Kernan et al., 1986; Korngold et al., 1987). The precise nature of these cells and the mechanisms they use are understood in greater detail (discussed below). Second, the recipient must be incapable of rejecting the transplanted cells (immunocompromised). A patient with a normal immune system will usually reject cells from a foreign donor. In allogeneic BMT, the recipients are usually immunosuppressed with chemotherapy and/or radiation before stem cell infusion (Welniak et al., 2007). Third, the recipient must express tissue antigens that are not present in the transplant donor. This area has been the focus of intense research that has led to the discovery of the major histocompatibility complex (MHC; Petersdorf and Malkki, 2006). Human leukocyte antigens (HLA) are proteins that are the gene products of the MHC and that are expressed on the cell surfaces of all nucleated cells in the human body. HLA proteins are essential to the activation of allogeneic T cells (Petersdorf and Malkki, 2006; Krensky et al., 1990) discussed below. This chapter on **mouse models** of acute GVHD will place the immuno-biological mechanisms of Billingham's postulates in perspective.

In addition to these seminal postulates on GVH reaction, the critical requirement of immune cells from the donor graft for optimal leukemia/tumor elimination: a process called graft-versus-leukemia (GVL) effect, and its tight link with GVHD were initially made from **mouse models** (43). Other **models** such as the canine, nonhuman primate, and rat **models** also played important roles, particularly in the development of clinically used immuno-suppressants. Nonetheless, the presence of well-characterized in-bred strains, availability of knock-out and transgenic animals, easy availability of reagents, and the relative low cost have made **mouse models** the most utilized systems for investigating the mechanisms of GVH responses.

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Overexpression of tissue inhibitor of metalloproteinases-3 in intestinal and cutaneous lesions of graft-versus [Mod Pathol. 2003]

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