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Mouse Models of Bone Marrow Transplantation

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ABSTRACT

Over the last 50 years, mouse models of bone marrow transplantation have provided the critical links between graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) pathophysiology and clinical practice. The initial insight from mouse models that GVHD and GVL were T cell dependent has long been confirmed clinically. More recent translations from mouse models have included the important role of inflammatory cytokines in GVHD. Newly developed concepts relating to the ability of antigen presenting cell (APC) and T cell subsets to mediate GVHD now promise significant clinical advances. The ability to use knockout and transgenic approaches to dissect mechanisms of GVHD and GVL mean that mouse systems will continue as the predominant preclinical platform. The basic transplant approach in these models, coupled with modern "real-time" immunologic imaging of GVHD and GVL is discussed.

KEY WORDS

Allogeneic • GVHD • GVL

MOUSE MODELS OF GVHD

Historic Perspectives

Bone marrow transplantation (BMT) was conceived in the early 1950s out of rodent studies focusing on the effects of radiation. These now classical experiments noted that shielding of the spleen, or infusion of bone marrow from a "donor animal" could protect animals from lethality [1,2]. Interestingly, this protection was initially thought to be because of the transfer of a humoral factor until subsequent chromosomal analysis confirmed the engraftment of donor cells in 1956 [3]. Even at this time, the presence of a graft-versus-leukemia (GVL) effect was mooted [4]. A report of clinical transplantation followed a year later by E. Donnel Thomas and colleagues [5], and the field was born. Over the subsequent decade the introduction of rudimentary tissue typing paved the way for the classical murine studies of Korngold and Sprent [6,7] in the 1970s, which confirmed the T cell dependence of GVHD. Indeed, much of our current understanding of BMT has its origin in their subsequent studies that determined the role of T cell subsets in GVHD across various MHC [8] and minor histocompatibility (HA) mismatches [9].

Mouse Models of GVHD

MHC mismatched or matched. Current murine models of BMT can be broadly grouped into those in which GVHD is directed to MHC (class I, class II, or usually both) or to isolated multiple minor HA alone. Although multiple minor HA mismatches also exist in the former, their impact is usually limited relative to that induced by full MHC disparities. The GVHD that develops in response to a full (class I and II) MHC disparity is dependent primarily on CD4 T cells, although CD8 T cells can provide additive pathology. These systems, by virtue of their CD4 dependence, result in an inflammatory "cytokine storm," capable of inducing GVHD in target tissues without the requirement for cognate T cell interaction with MHC on tissue [10]. The BMT models in which GVHD is directed to mutated class I (bm1) or class II (bm12) MHC antigens in isolation represent well-utilized systems where GVHD is mediated only by CD8 or CD4 T cells, respectively. The parent to F1 models (eg, B6 → B6D2F1) offer the advantage of eliminating T cell-dependent host-versus-graft rejection responses (NK-dependent "hybrid resistance" remain), and so are particularly useful if one is attempting to eliminate this as a variable across groups (eg, comparing the intensity of conditioning regimes on GVHD severity independent of differential engraftment kinetics) [11]. The induction of GVHD to multiple minor HA results in a process where either CD8 T cells, CD4 T cells, or both may play a role in disease [9]. In contrast to CD4-dependent GVHD, CD8 T cells induce GVHD primarily by their cytolytic machinery, which requires the TCR to engage MHC on target tissue [10]. Importantly, these CD4 versus CD8-dependent GVHD models will have differing requirements for antigen presentation. Either host or donor antigen-presenting cells (APC) will be able to initiate CD4-dependent GVHD [12], whereas only host APC will induce GVHD in CD8-dependent systems [13]. Although the minor HA disparate systems may be the most appropriate models of clinical BMT, the MHC disparate systems can also induce the full spectrum of clinically relevant GVHD while permitting greater dissection of immunologic mechanisms because of the enhanced ability to measure immunologic pathways of GVHD both in vivo and ex vivo. Thus, it is critical from the outset to understand what questions are being asked so that the most relevant BMT model can be chosen (summarized in Table 1).

Conditioning intensity and T cell doses. Inbred mouse strains are variably sensitive to radiation, and so maximal tolerated doses (primarily delivered in 2 split fractions within a day at <150 cGy/min) differ from strain to strain. As a general rule, B6 are more resistant that BALB/C mice, and F1 more resistant than parental strains. Thus, the maximal tolerated total body irradiation (TBI) dose (ie, that which will allow universal survival following transplantation of syngeneic or T cell-depleted (TCD) allogeneic grafts) is approximately 900 cGy for a BALB/C mouse relative to 1500 cGy for a B6D2F1 mouse. Generally, the higher the TBI dose, the earlier and greater the intensity of the inflammatory arm of GVHD [14]. By contrast, BMT models utilizing low TBI doses and high donor T cell doses will result in GVHD dominated by later onset T cell-dependent pathology. This is particularly important when studying inflammatory mediators of GVHD, as inhibitors may have little effect in BMT models utilizing low TBI and high donor T cell doses, potentially giving rise to false negative results. Conversely, this system may be ideally suited to studying inhibitors of T cell effector function. BMT models using non-TBI-based conditioning have been limited, primarily because of the ease of TBI delivery and its clear clinical relevance. Nevertheless, cyclophosphamide, fludarabine, and busulphan can be delivered in mouse systems, and this may become important to model clinical nonmyeloablative transplantation. Certainly, the addition of these agents to TBI in mouse models can cause a dramatic enhancement of GVHD severity and alteration of effector pathways [15].

Models of acute versus chronic GVHD (aGVHD, cGVHD). Unlike aGVHD models, the induction of clinically relevant cGVHD in BMT models using (nonmutated) inbred strains has been challenging. Perhaps the most relevant is the B10.D2 → BALB/C system, originally described as a model of scleroderma in which grafts are transplanted following sublethal (600 cGy) doses of TBI [16,17]. In our experience, a similar and more penetrate spectrum of disease also develops using lethal TBI doses in conjunction with low doses

Table 1. *Commonly Used Mouse Models of BMT*

Donor	Host	Usual TBI Dose (cGy)	GVHD Targets	T cell Dependence	Lethality
Acute GVHD models					
B6	(B6 × DBA/2)F1	1100-1500	I, II, mHAs	CD4 (±CD8)	Major
B6	BALB/c	900	I, II, mHAs	CD4 (±CD8)	Major
BALB/c	B6	1100	I, II, mHAs	CD4 (±CD8)	Major
B6	bm1	1100	I	CD8	Minimal
B6	bm12	1100	II	CD4	Minor
C3H.SW	B6	1100	mHAs	CD8	Minimal
B6	BALB/b	900	mHAs	CD4	Major
B10.D2	DBA/2	1000	mHAs	CD4	Major
DBA/2	B10.D2	1000	mHAs	CD8	Minor
B10.BR	CBA	1100	mHAs	CD8	Major
Chronic GVHD models					
B10.D2	BALB/c	600-900	mHAs	CD4	Minor
LP/J	B6	1100	mHAs	CD4	Minor
DBA/2	B6D2F1	Nil	I, II, mHAs	CD4	Minor
B6	(B6 × BALB/c)F1	Nil	I, II, mHAs	CD4	Minor
BALB/c	(BALB/c × A)F1	Nil	I, II, mHAs	CD4	Minor

Donor and host strains used in common BMT models, usual total body irradiation (TBI) doses (delivered in two split doses on a single day at <150 cGy/min), target GVHD antigens—MHC class I (I), MHC class II (II)—or minor HA (mHA), T cell dependence of subsequent GVHD (CD4 and/or CD8), and intensity of GVHD lethality (Major ≥50% mortality, Minor = 10% to 50% mortality, Minimal = <10% mortality) over 6 weeks. TBI doses and lethality will differ depending on recipient pathogen load/animal facility.