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GVHD pathophysiology: is acute different from chronic?

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Graft-versus-host disease (GVHD) is the major complication of allogeneic hematopoietic cell transplantation (HCT). GVHD occurs in acute and chronic forms. Acute GVHD usually manifests within 100 days following HSCT. It is induced by donor T cells responding to the mismatched host polymorphic histocompatibility antigens. Chronic GVHD generally manifests later (>100 days) and has some features of autoimmune diseases. It may develop either de novo or following resolution of – or as an extension of – acute GVHD. Chronic GVHD is also thought to be induced by donor T cells, but the nature of relevant antigens, the critical cellular subsets and the mechanisms of chronic GVHD remain less well understood. In this chapter we briefly discuss and contrast the pathophysiologies of acute and chronic GVHD.

Key words: allogeneic hematopoietic stem cell transplantation; antigen-presenting cells (APC); T cells; cytokines; minor histocompatibility (miHAs).

The number of allogeneic hematopoietic cell transplantations (HCTs) continues to increase, with more than 20,000 allogeneic transplantations performed annually. The graft-versus-leukemia/tumor (GVL) effect following allogeneic HCT effectively eradicates many hematological malignancies.[1] Improvements in infectious prophylaxis, immunosuppressive medications, supportive care and better donor selection have

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contributed to improved outcomes after allogeneic HCT.[1] Yet the major complication of allogeneic HCT, graft-versus-host disease (GVHD), remains lethal and limits its wider application.[2] Traditionally, clinical GVHD occurring prior to 100 days after HCT is called acute, and that occurring after 100 days is called chronic GVHD.[3–5] It is important to recognize that this traditional definition was based on the temporal rather than the clinical or pathophysiological nature of GVHD. This definition is not satisfactory, because acute and chronic GVHD have distinct clinical features that can sometimes present concomitantly and/or independently of the time after transplant. A recent National Institutes of Health (NIH) consensus classification of GVHD includes late-onset (after day 100) acute GVHD and an overlap syndrome that has features of both acute and chronic GVHD.[6]

The clinical manifestations of acute GVHD occur in the skin, gastrointestinal tact and liver.[7] Pathologically, the sine qua non of acute GVHD is selective epithelial damage of target organs.[8,9] It typically manifests within 20–40 days following full-intensity allogeneic HCT, and may be slightly more delayed following reduced-intensity allogeneic HCT.

Chronic GVHD is a syndrome that typically presents more than 100 days after transplant; it can occur either as an extension of acute GVHD (progressive), or after a disease-free interval (quiescent), or with no precedent (de novo) acute GVHD.[4–6,10] It is important to note that strategies which have improved acute GVHD rates – such as cord-blood transplants – have not as clearly affected the incidence of chronic GVHD.[11] Additionally, strategies that have not significantly altered acute GVHD rates – such as peripheral blood stem cell transplants (PBSCTs) – appear to have increased the incidence of chronic GVHD.[12] Chronic GVHD has myriad manifestations, and unlike acute GVHD it can affect multiple organ systems. In general, it can present as lichen-type features, dryness, strictures or sclerosis of the several organs including skin (sclerosis), mouth (xerostomia), eyes (xerophthalmia), vagina, esophagus, liver, lung (bronchiolitis obliterans), fasciitis, serositis (including pericardial or pleural effusions), and rarely kidneys (nephrotic syndrome).[6,13] Pathologically, depending on the severity, a plethora of features are observed. However, in contrast to acute GVHD, it is most often characterized by fibrosis of the affected organ.[14]

The discordance between acute GVHD rates and chronic GVHD, the time of onset, the organ system involvement, types of tissue damage, the differences in clinical features, and the kinetics suggest that although both acute and chronic GVHD occur after allogeneic HCT, the underlying immunopathological mechanisms might be distinct. The pathophysiology of acute and chronic GVHD based on clinical data and experimental studies is discussed below.

PATHOPHYSIOLOGY OF GVHD

Rapid advances have allowed for refinements of the model that was proposed several decades ago by Billingham for the development of GVHD.[15] The availability of several experimental models that reflect the early GVH process has substantially enhanced our understanding of the biology of acute GVHD.[16] Target-tissue damage in acute GVHD is caused by cytopathic donor T cells that respond to the genetically disparate host polymorphic antigens, which are presented by host and/or donor antigen-presenting cells (APCs). This damage is further amplified by the non-specific inflammatory mediators. This is now conceptualized to occur in sequential phases involving complex

interactions between a variety of cytokines, chemokines, adaptive and innate immune subsets (summarized in several excellent recent reviews).[2,17–19]

Similar advances in the understanding of the biology of chronic GVHD have not been made, in part due to the absence of appropriate experimental models that mimic all the features of chronic GVHD. Some murine models – depending on the strain combinations (the type of genetic disparity), conditioning regimen, and type and amount of donor cells – produce certain features of chronic GVHD, such as the fibrosis of skin, lung or lupus nephritis or liver damage.[12] But no single model captures all of the features and kinetics of chronic GVHD. This lack of appropriate experimental models might be because of the differences between humans and experimental species. For example, in contrast to murine models, the kinetics of clinical chronic GVHD in humans is slower and is observed only after prophylaxis and/or treatment for acute GVHD. Even when clinical chronic GVHD arises de novo and in the absence of active immunosuppression, it is not possible to definitively rule out the impact of either GVH prophylaxis and/or subclinical acute GVHD on the subsequent development of chronic GVHD. It is therefore important to consider these caveats when attempting to understand the biology of chronic GVHD from experimental models. The genetic and immunological basis of acute and chronic GVHD biology is discussed below.

GENETIC BASIS OF GVHD

Human leukocyte antigens (HLA) matching

The most important immunogenic proteins that contribute to the intensity of GVH reaction are the human leukocyte antigens.[20] HLA proteins are highly polymorphic and are encoded by the major histocompatibility complex (MHC). Class I (HLA-A, -B, and -C) antigens are expressed on almost all nucleated cells. Class II antigens (DR, DQ, and DP) are primarily expressed on hematopoietic cells, but their expression can be induced in many other cell types following inflammation or injury.[20] Several lines of evidence demonstrate that regardless of the type of graft or the intensity of the preparative regimen, acute GVHD is directly related to the degree of HLA mismatch (approximately 40% in recipients of HLA-identical grafts but increases to 60–80% in recipients of unrelated or one-antigen HLA-mismatched grafts).[21–25] These clinical observations have been validated in experimental models wherein acute GVHD leading to rapid mortality is observed across many MHC disparate strain combinations.[16]

Although the role of HLA disparity has been analyzed in the overall outcomes after allogeneic HCT, relatively fewer studies have attempted to correlate it with the incidence and severity of chronic GVHD. Some clinical studies have demonstrated a direct association between HLA-A, -B, -C (class I) disparity and chronic GVHD.[26–28] In contrast to acute GVHD, only a few MHC-mismatched animal models recapitulate some features of chronic GVHD. A recent study demonstrated that acute GVHD in an MHC-mismatched model resulted in the emergence of donor-reactive donor T cells in the host, which caused severe 'autoimmune' colitis upon adoptive transfer back into donor but not host type mice.[29] Collectively, these observations nonetheless make a strong case for the critical role of HLA disparity in both acute and chronic GVHD. However, it remains to be determined whether specific mismatches are more critical for chronic than acute GVHD.

Minor histocompatibility antigen (miHAs)

In the context of MHC-matched HCT, as is the case with most clinical allo-HCT, donor T cells recognize MHC-bound peptides derived from the protein products of polymorphic genes (minor histocompatibility antigens, miHAs) that are present in the host but not in the donor.[30–36] The critical role of miHA disparity for the development of acute GVHD has been demonstrated by the development of acute GVHD in substantial numbers of patients (40%) receiving HLA-identical grafts and optimal post-grafting immune suppression.[33,37] The pattern of expression of miHAs might account for the unique target organ involvement in acute GVHD.[31,37] This notion is supported by experimental murine studies, which show that distinct miHAs dictate the phenotype and target organ involvement of acute GVHD.[38] Experimental data have demonstrated that not all of the miHAs are equal in their ability to induce lethal GVHD, and that they show hierarchical immunodominance.[39,40] Disparity in a single immunodominant miHA is not sufficient to cause acute GVHD, although T cells targeting single miHA can induce tissue damage in a human skin explant model.[41,42] However, to date no specific miHAs that are common and have equivalent immunogenicity in most patients have been identified. Nonetheless, the polymorphic miHAs are the critical antigenic targets for inducing acute GVHD in MHC-matched HCT.

By contrast, on the basis of its clinical features, chronic GVHD has been considered to be an 'autoimmune' disease. Some experimental studies have shown that T cells from animals with chronic GVHD are specific for a common (shared between host and donor) determinant of MHC class II molecules[43,44], and are therefore considered to be 'autoreactive'. These autoreactive cells of chronic GVHD are associated with a damaged thymus and negative selection.[7,45–48] This would then indicate that the non-polymorphic antigens expressed in donor and recipient rather than the disparate polymorphic miHA antigens are the likely targets in chronic GVHD. Despite the experimental evidence and clinical similarity to autoimmune diseases, there are no clear clinical data on the isolation of donor-derived T cell clones that recognize non-polymorphic antigens from both donor and recipient.

By contrast, emerging clinical data show a strong correlation between the presence of immune responses against ubiquitously expressed miHAs and chronic GVHD. Furthermore, because chronic GVHD occurs (a) only after allogeneic HCT, (b) acute GVHD is its main risk factor[12],and (c) is distinct from 'syngeneic' GVHD caused by improper thymic selection[48], it is possible that chronic GVHD is caused by T cells that have undergone chronic antigen stimulation due the presence of ubiquitous miHA antigens. The similarity to clinical features of 'autoimmune' diseases might therefore be the result of chronic stimulation-induced target organ damage, which perhaps happen to be miHAs for chronic GVHD and non-polymorphic 'auto-antigens' for autoimmune diseases. This concept is supported by the recent observations in female-to-male HCT demonstrating a strong correlation with the presence of antibodies to Y-chromosome-encoded histocompatibility antigens and chronic GVHD.[49,50] In any event, even if miHA are the targets, it remains unknown whether these are the same as the ones targeted in acute GVHD. A recent elegant murine study in fact suggested that the type and selection of immunodominant miHAs determines the target and character of GVHD damage.[38]

Lastly, because of 'epitope spreading' and the failure of appropriate regulatory mechanisms – either as a consequence of acute GVHD or its treatment and/or prophylaxis – it is also conceivable that donor T cells which recognize both

non-polymorphic and miHA epitopes might cause and perpetuate chronic GVHD. Thus, in contrast to the antigenic targets for acute GVHD, the nature of the relevant immunogenic targets for chronic GVHD remains, as yet, largely speculative.

KIR and cytokine polymorphisms

The role of human killer-cell immunoglobulin-like receptors (KIRs) has been a focus of intense study in recent years.[20,51,52] Polymorphisms in the transmembrane and cytoplasmic domains of KIR receptors govern whether the receptor has inhibitory potential or activating potential, and the balance between them regulates NK cell activation.[53] Recent experimental data and some clinical observations suggest that KIR mismatch in GVH direction is associated with GVL without exacerbation of acute GVHD, while some others have not shown any clear association.[20,51,52,54,55] There is a paucity of both experimental and clinical data on the role of KIR mismatches and outcomes of chronic GVHD.

Several cytokines, such as interleukins IL-1, IL-6, IL-8, tumor necrosis factor α (TNFα), released during the 'cytokine storm' phase of acute GVHD, play a critical role in amplifying acute GVHD.[18] Gene polymorphism studies with TNF, IL-10, interferon γ (IFNγ) variants have correlated with acute GVHD in some but not all studies.[56–58] Genetic polymorphisms of proteins involved in innate immunity, such as NOD2/CARD15, in both the donors and recipients were recently shown to have a strong association with acute gastrointestinal GVHD.[59] Despite the obvious inflammatory state of chronic GVHD, there are no clear experimental data on the role of proinflammatory cytokines in chronic GVHD, although increased levels of TNFα and IFNγ transcription might predict the onset of extensive chronic GVHD.[60]

Despite the lack of experimental data, some clinical studies have evaluated the role of certain donor and recipient cytokine polymorphisms. These studies showed that IL-10, IL-1α, IL-1Ra and IL-6 polymorphisms have shown variable association with chronic GVHD.[58] A common problem with most of these studies is the heterogeneity and the small numbers of patients. Nonetheless these data, when taken together, suggest that both acute and chronic GVHD are likely to be modulated by non-HLA polymorphisms in addition to mismatched HLA and miHAs.

Thus genetic variation in both patient and donor can significantly affect both acute and chronic GVHD by causing disparity of transplant antigens and modulating the intensity of the immune responses by alteration of the activation and function of several immune cells, as discussed below.

IMMUNE-CELL SUBSETS IN GVHD

APCs in GVHD

The earliest phase of acute GVHD is set in motion by the damage caused by the underlying disease and the conditioning regimens that cause multiple changes and enhance the secretion of proinflammatory cytokines such as TNFα and IL-1.[61–66] This results in activation of host APCs which is further amplified by the systemic translocation of immunostimulatory microbial products such as lipopolysaccaride (LPS).[62,67–69] This scenario is concordant with the clinical observation that the risk of GVHD increases with conditioning regimens that cause extensive injury to epithelial and endothelial surfaces[62,66], and has been supported by elegant murine studies.[63]

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