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The Biology of Chronic Graft-versus-Host Disease: A Task Force Report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease

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A B S T R A C T

Chronic graft-versus-host disease (GVHD) is the leading cause of late, nonrelapse mortality and disability in allogeneic hematopoietic cell transplantation recipients and a major obstacle to improving outcomes. The biology of chronic GVHD remains enigmatic, but understanding the underpinnings of the immunologic mechanisms responsible for the initiation and progression of disease is fundamental to developing effective prevention and treatment strategies. The goals of this task force review are as follows:

- Summarize the current state of the science regarding pathogenic mechanisms of chronic GVHD and critical knowledge gaps.
- Develop working hypotheses/overriding concepts for chronic GVHD development.
- Define the usefulness of current preclinical models to test working hypotheses and ultimately discover and develop new therapeutic strategies.
- Identify shortcomings of preclinical models, and define criteria for the creation of additional models to address these limitations.

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This document is intended as a review of our understanding of chronic GVHD biology and therapies resulting from preclinical studies, and as a platform for developing innovative clinical strategies to prevent and treat chronic GVHD.

INTRODUCTION

Relapse of underlying malignancy and the development of chronic graft-versus-host-disease (GVHD) remain the major obstacles to improving outcomes following allogeneic hematopoietic cell transplantation (HCT). Chronic GVHD remains the prevailing cause of nonrelapse mortality in patients surviving longer than 2 years after allogeneic HCT, negatively influencing both quality of life and long-term outcomes. Unfortunately, the incidence and severity of chronic GVHD have increased over the last decade despite advances in clinical practice [1,2]. Thus, although many GVHD prevention regimens have reduced acute GVHD, chronic GVHD amelioration has been less affected [3-5], with exceptions seen with the use of antilymphocyte antibodies and high-dose cyclophosphamide in the early post-transplantation period [6-9]. Unlike acute GVHD, which is driven almost exclusively by the activation of donor T cells and the release of proinflammatory cytokines [10], the immunopathophysiology of chronic GVHD is more complex. Chronic GVHD involves multiple, distinct interactions among alloreactive and dysregulated T and B cells and innate immune populations, including macrophages, dendritic cells (DCs), and neutrophils, that culminate in the initiation and propagation of profibrotic pathways.

Over the past decade, the National Institutes of Health's consensus criteria for the diagnosis and scoring of chronic GVHD have brought consistency to the terminology and methods for reporting assessment findings in HCT recipients [11,12]. This effort has been successful in standardizing the language and documentation used by clinicians to describe clinical manifestations of disease [13-15], yet the precise mechanisms responsible for the onset and progression of chronic GVHD remain elusive. In this paper, we review the current understanding of the immunology of chronic GVHD and provide guidance for pursuing several focused areas of research over the next decade.

CLINICAL MANIFESTATIONS OF CHRONIC GVHD

Chronic GVHD presents with the following key clinical manifestations: mucocutaneous, myofascial, pulmonary, and "other," affecting essentially any organ system in the body. Characteristic features may include chronic inflammatory changes that can be relatively acellular involving ocular [16], oral, esophageal, skin, joint and fascial, and genital [12] tissues. Progression to clinically significant fibrosis involving multiple organs in the integumentary, musculoskeletal, aerodigestive, gastrointestinal, cardiorespiratory, reproductive, and peripheral nervous systems occurs in severely affected individuals. Rare but severe clinical presentations of chronic GVHD also can include polyserositis (with pericardial and pleural effusions) or polymyositis with severe muscle weakness and elevated muscle enzyme levels [17].

Because scoring is based on the degree of tissue involvement and functional impairment and not on the underlying biology, clinical disease classifications are unlikely to help translational scientists complete association analysis of large datasets. This is particularly complicated by the strong correlations between chronic GVHD and other late complications, including metabolic syndrome, renal impairment, infections, and the development of second cancers [18-20].

Standardizing Clinical Disease Nomenclature to Facilitate Interpretation of Biological Studies of Chronic GVHD

The transplantation biology field seeks approaches to establish clinical tolerance, defined as a specific lack of immune activity to donor and host tissues with preservation of responses to foreign antigens, such as invading pathogens [21]. Tolerance could be achieved through mitigation of T cell reactivity, a process that typically occurs through 2 mechanisms, central (thymic) tolerance and peripheral (extrathymic) tolerance [22]. Known requirements for the induction or description of tolerance after HCT in the clinic are lacking. Chronic GVHD is the net result of an imbalance between relatively higher immune effector mechanisms that cause inflammation and disease and lower inhibitory (regulatory) mechanisms that may maintain tolerance (Figure 1).

The interpretation of biological studies of chronic GVHD is complicated by variability in the classification of different manifestations of disease. A rational approach for grouping patient samples is required for studies of human immune cell function. Deciphering the biology of clinical chronic GVHD and interpreting correlative biology studies conducted in affected patients is both important and challenging because of the grouping of diverse patient subsets (eg, established chronic GVHD with newly diagnosed de novo with overlap, controls with/without previous acute GVHD or with/without subsequent chronic GVHD) that customarily occurs in the context of clinical investigation. A single nomenclature and comparisons among similar clinical groups should be used (Table 1). Moreover, the biology of chronic GVHD is likely different in newly diagnosed patients (at the onset of active disease) compared with that observed later in the disease course. Thus, grouping all chronic GVHD patients together in biological analyses should be avoided whenever possible. Instead, we propose grouping chronic GVHD patients according to the presumed underlying biology that consists of inflammatory, immune dysregulatory (functionally nontolerant), or fibrotic/sclerotic manifestations (Table 2), and noting the duration of the disease.

Similarly, definitions of nomenclature regarding the terms "alloreactivity" and "autoreactivity" require consistent use. In this paper, we refer to all donor T cell responses as alloreactive in nature when donor cells respond to recipient cells and autoreactive when donor immune response occur against donor cells, such as platelets or red blood cells. Both responses are part of the spectrum of chronic GVHD, and the term "autoantibodies" has been used to describe tissue reactive alloantibodies. These definitions have caveats given the possible contribution of donor-derived antigen-presenting cells (APCs) to the T cell activation that contributes to chronic GVHD [23,24].

Factors Influencing the Development of Chronic GVHD and the Interpretation of Biological Studies

A number of clinical variables are associated with the development of chronic GVHD and may influence the underlying pathophysiology of the disease. These include, but are not