ELSEVIER

Clinical and Applied Immunology Reviews 5 (2005) 95–109

Clinical and Applied Immunology Reviews

Minor Histocompatibility Antigens: Molecular targets for immunomodulation in tissue transplantation and tumor therapy

Subramaniam Malarkannan, Jeyarani Regunathan, Angela M. Timler

Laboratory of Molecular Immunology, Blood Research Institute, Blood Center of Southeastern Wisconsin and Division of Neoplastic Diseases, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI 53226

Received 11 May 2004; received in revised form 3 September 2004; accepted 16 September 2004.

Abstract

Even after matching the alleles for the major histocompatibility complexes (MHC), grafts are rejected in a considerable percentage of transplant recipients by the host immune system. In these patients, the host T cells recognize unique antigenic peptides on the cells from the transplanted grafts. These peptides are different from that of hosts due to non-MHC polymorphic differences between the host and the donor. To distinguish between the MHC and these, they were termed minor histocompatibility (mH) complexes. Thus, mH antigens (mH-Ags) are historically defined as allo-peptides derived from allelic gene products that are capable of eliciting T cell responses. Because of their significance in determining the clinical outcome of graft acceptance and graft-versus-host disease (GvHD), mH-Ags have been intensively studied for decades. Also, a strong T cell mediated immune response to mH antigenic peptides has the potential for formulating adoptive cellular immunotherapy for patients with hematological malignancies (Graft-versus-Leukemia, GvL). Utilizing recent technological advances the identities of many human and murine mH antigenic peptides have been defined towards achieving clinical applications. These antigenic peptides are currently being evaluated in clinical or basic immunological studies for their ability to produce effective T cell responses. Furthermore, to our surprise recent studies have revealed that some of the full-length mH proteins-themselves may possess specialized immune functions. This novel discovery is dictating a paradigm shift to redefine the functionality of mH-Ags. Given that the novel immune regulatory functions of mH-Ags can also be harnessed; the possibilities to formulate additional cancer immunotherapies are expanding.

Abbreviations: mH-Ag, Minor antigen; GvHD, Graft versus Host Disease; Gvl, Graft-versus-Leukemia; MHC, Major Histocompatibility Complex; HLA, Human Leukocyte Antigen; APC, Antigen Presenting Cells; HSCT, Hematopoietic Stem Cell Transplant; BMT, Bone Marrow Transplant.

Correspondence: Subramaniam Malarkannan, Blood Research Institute, Rm 214, Blood Center of Southeastern Wisconsin, Milwaukee WI 53226-2178 Tel: (414) 937 3812, Fax: (414) 937 6284.

E-mail address: smalarkannan@bcsew.edu (S. Malarkannan).

1529-1049/05/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi: 10.1016/j.cair.2004.09.002

1. Introduction

Minor histocompatibility antigens (mH-Ags) are an immunological hurdle against the successful tissue transplantation. Pioneering studies performed half-a-century ago by George D Snell, formed the basis to differentiate between the major (MHC) and the minor histocompatibility antigens (mH-Ags) [1]. The ability to type HLA molecules was a significant milestone in matching donors and recipients as it greatly reduced the risk of allogenic rejection. Less frequently but in considerable clinical instances, even after HLA matching, non-MHC polymorphism played a role in graft rejections. Similar tissue rejections are also observed among syngeneic animals, which have identical H2 haplotypes, but are otherwise genetically different [2]. Extensive studies both in the case of mice and human for the past five decades, demonstrated that these rejections are rather caused by polymorphism exhibited in *mH* loci [3–6]. Unlike the H2/HLA, mH-Ags are defined by immunogenic peptides that are generated from their full-length proteins. In addition to foreign (i.e., viral, bacterial) and neo antigens (tumor), the mH-Ags have also been characterized as 8–14 amino acid long peptides, bound to the H2/HLA molecules (MHC) that are displayed on the surface of antigen-presenting cells (APCs). These peptide/MHC complexes are recognized by host T-cells, which play a vital role in the rejection of the transplant. While the T-cells in the host body are expected to recognize and eliminate virally infected or transformed tumor cells, the rejection of an H2/HLA identical graft by the recipient body was a clinical puzzle for a long time. The answer has been found to reside in the polymorphism of *mH* loci and their variant protein products.

When mH-Ags were first defined, they were thought of as full-length cell surface proteins participating in immune activation in particular relevance to T cells [1,2]. Studies in the past decade demonstrated that the immune responses generated against mH-Ags are indeed mediated by T cells and directed to short peptides presented in the context of H2/HLA. To our surprise, recent findings have illustrated another facet of mH-Ags. Apart from providing short peptides, the full-length mH-Ags proteins also possess specific cellular, immune and oncogenic functions. Some of these functions ascribed to specific full-length mH proteins have started making changes in the definition and clinical applications of mH-Ags. Recent progresses made in defining murine and human mH-Ags, their use in both basic and applied clinical immunology are discussed in this review.

2. Discovery of mH-Ags

More than 100 years worth of experimentation in transplant biology has resulted in a fundamental understanding of several facets of immunology, including the discovery and characterization of the *MHC* and several *minor H* loci. Over five decades ago, George D. Snell along with Peter A Gorer originally described transplantation (histocompatibility, H) antigens as those that elicited rejection of skin or tumor grafts from genetically non-identical donors [7]. In this quest to characterize the genes responsible for these antigens, Snell identified several unique loci and identified one locus that caused a marked rapid rejection, whereas all others led to slower rejection over a period of longer time points. He named the product of this locus, *H2*, *H* standing for histocompatibility. *H2* is a complex of genes in mice characterized as the classical major histocompatibility complex (MHC) that binds to short antigenic peptides and presents them to T-cells. Pioneering studies on the