Clinical Immunology (2012) 143, 99–115

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

REVIEW

Immunodominance: A pivotal principle in host response to viral infections☆

Ali Akram*, Robert D. Inman**

University of Toronto, Institute of Medical Science and Department of Immunology, Toronto, Canada M5S1S8
Toronto Western Hospital, University Health Network, Department of Genetics and Development, Toronto, Canada M5T2S8

Received 16 December 2011; accepted with revision 28 January 2012
Available online 10 February 2012

KEYWORDS
Immunodominance;
Immunodominant peptide;
MHC class I;
Host immune response;
Influenza infection;
HIV infection

Abstract We encounter pathogens on a daily basis and our immune system has evolved to mount an immune response following an infection. An interesting phenomenon that has evolved in response to clearing bacterial and viral infections is called immunodominance. Immunodominance refers to the phenomenon that, despite co-expression of multiple major histocompatibility complex class I alleles by host cells and the potential generation of hundreds of distinct antigenic peptides for recognition following an infection, a large portion of the anti-viral cytotoxic T lymphocyte population targets only some peptide/MHC class I complexes. Here we review the main factors contributing to immunodominance in relation to influenza A and HIV infection. Of special interest are the factors contributing to immunodominance in humans and rodents following influenza A infection. By critically reviewing these findings, we hope to improve understanding of the challenges facing the discovery of new factors enabling better anti-viral vaccine strategies in the future.

Abbreviations ImDc, immunodominance; ImD, immunodominant; SbD, Subdominant; Flu, Influenza A; HIV, Human immunodeficiency virus; Tg, transgenic; TCR, T cell receptor; pMHC, peptide/MHC class I complex; CTL, cytotoxic T lymphocyte; APCs, Antigen presenting cells; HLA, Human leukocyte antigen; DKO, double knock-out; NP, Nucleoprotein; Vβ, variable beta

☆ This work was supported by scholarships received by Ali Akram [M.Sc., Ph.D. (c)] from the Arthritis Centre for Excellence (ACE) and Queen Elizabeth II Graduate scholarship in Science and Technology (QEII-GSST) from University Health Network and University of Toronto. Ali Akram is also supported by a CIHR grant received by Dr. Robert D. Inman.

* Correspondence to: A. Akram, University of Toronto and University Health Network (UHN), Toronto Western Hospital, 399 Bathurst Street, Room13-415, Toronto, Ontario, Canada M5T-2S8.
** Correspondence to: R.D. Inman, University of Toronto and University Health Network (UHN), Toronto Western Hospital, 399 Bathurst Street, Room1E-423, Toronto, Ontario, Canada M5T 2S8. Fax: +1 416 603 4348.
E-mail addresses: Ali.Akram@utoronto.ca (A. Akram), Robert.inman@uhn.ca (R.D. Inman).

1521-6616/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.clim.2012.01.015

Contents

1. Introduction

On a daily basis we come into contact with wide range of pathogens. These potentially pathogenic encounters may be airborne or by direct contact. In some cases proximity to particular pathogens determines whether infection will ensue. Examples of airborne diseases include anthrax and flu. In the case of acquired immune deficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV), transmission is predominantly by way of body fluid exchange through sexual contacts. Overall, some potential pathogens are harmless and may be 'ignored' by our immune system, whereas other pathogenic encounters can cause a robust immune response involving both the innate and the adaptive arms of the immune system.

Innate immunity is the first line of defense against pathogens. Upon infection, key elements of innate immunity, such as macrophages and neutrophils, may successfully limit and non-specifically clear pathogens by inducing acute inflammatory responses, including IFN-γ production. This process allows the adaptive immunity to mount a more specific response 4 to 5 days post-infection. B and T lymphocytes along with dendritic cells (DC) are amongst the central elements of adaptive immunity. Following an infection, a complex multi-step sequence involving the processing of different proteins leads to generation of antigenic peptides. These peptides are then presented on the cell surface by major histocompatibility complex (MHC) class I and II molecules. MHC class I molecules mostly present peptides derived from cytosolic proteins. Viral proteins provide an important source of foreign peptides presented by MHC class I molecules. While it was assumed for some time that endogenous peptides were only presented by MHC class I and exogenous peptides by MHC class II, recent findings [1–4] have shown that class I molecules are also capable of presenting exogenous peptides through cross presentation.

The crucial first step in adaptive immunity following viral infection is the activation of naive antigen-specific T cells by antigen presenting cells (APCs) in the lymphoid organs. During T cell development thymocytes undergo a complex process involving both positive and negative selection. The cells surviving these selection processes mature into naive T cells. These T cells respond to viral antigens only if they are presented peptides in the context of self-MHC molecules (i.e., pMHC) on the surface of APCs [5]. Both the MHC molecule and its bound peptide have to be recognized by specific T cell receptors (TCR) in order to initiate T cell activation [5]. Interactions of co-stimulatory molecules with their ligands also contribute to the overall T cell activation following initial pMHC–TCR interaction.

$CD8^+$ T cell activation is initiated by the interaction of a TCR–CD3 complex with a pMHC class I complex (i.e., pMHC-I) [6]. MHC class I proteins consist of a highly polymorphic heavy chain (HC) and monomorphic β_2-microglobulin (β_2m). The HC is made up of three extra-cellular domains (i.e., α_1, α_2 and α_3), a transmembrane domain (TM) and a cytoplasmic domain [5]. TCR makes contact with both α_1 and α_2 domains of the MHC class I molecule as well as its bound peptide, whereas CD3 helps in signal transduction