Available online at www.sciencedirect.com

SCIENCE DIRECT

Transplant Immunology 14 (2005) 171 – 174

Transplant Immunology

www.elsevier.com/locate/trim

Antigen processing is predictable: From genes to T cell epitopes

Stefan Stevanovic*

Universität Tübingen, Institut für Zellbiologie, Abteilung Immunologie, Auf der Morgenstelle 15, D-72076 Tübingen, Germany

Accepted 14 March 2005

Abstract

In order to induce a cellular immune response, antigens have to be processed in intracellular compartments, transported, and presented by HLA molecules prior to recognition by specific T cells. Many of the events that contribute to antigen processing have been thoroughly investigated during the past years and are now well understood, which lead to a number of prediction programs. "Reverse immunology" has been used for about 10 years in order to identify T cell epitopes from pathogens or tumor-associated antigens. The advantages and pitfalls of T cell epitope prediction compared to classical experimental procedures such as epitope mapping and cloning experiments have been discussed many times. In this presentation, a number of internet programs that offer help in T cell epitope prediction (or prediction of antigen processing) will be discussed in the light of transfusion medicine. Some databases are listing published HLA ligands and T cell epitopes, others offer epitope prediction for many HLA class I or class II restrictions. In addition, a number of established programs will be demonstrated which are freely accessible at no cost in the world wide web for the prediction of either HLA-peptide binding, proteasomal processing of antigens, or both. Epitope prediction and processing prediction programs will be applied to minor histocompatibility antigens (miHAgs) and compared. This reflects the actual possibilities and limitations of such computer-aided work not only in cellular immunology, but also in transplantation immunology.

Keywords: Antigen; Genes; T cell epitopes

1. Transplantation troubles the immune system

Canonical T cell reactions are directed against defined MHC/peptide complexes, whereby the MHC molecules are self and the peptide belongs to the nonself world [1]. When nature invented the adaptive immune system millions of years ago, her primary aim was resistance against small pathogens such as viruses or bacteria. At that time, transfusion or transplantation was unheard of. A sophisticated machinery was thus developed and constantly improved over eons to make pathogens stand out as conspicuously as possible for the effectors fighting against them, the most powerful actors nowadays are known as T cells. In transfusion medicine and during transplantation, however, modern medicine faces severe problems that are caused by the fact that the human immune system usually classifies other humans as foreign and consequently dangerous [2], just as human minds are sometimes prone to do. Such immune attacks that occur as graft rejection or graft-versus-host disease are somewhat irregular because they are mediated mainly by T cells that recognize nonself MHC irrespective of the presented peptide. Such alloreactions appear to be an artefact that was not taken into consideration during the original construction of the human immune system as an efficient means of defence.

In addition to alloreactions governed by the recognition of nonself MHC by T cells, a more modest variety of immune reaction against intra-species nonself has been observed. This "minor histocompatibility" effect [3] follows the classical rules of T cell recognition, which are HLA restriction and peptide dependency.

* Tel.: +49 7071 2987645; fax: +49 7071 295653.
E-mail address: stefan.stevanovic@uni-tuebingen.de.

0966-3274/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.trim.2005.03.018

2. Minor H reactions resemble canonical immune reactions

Human cells are used to display representative samples of their protein content as short peptides presented by HLA molecules on the cell surface (Fig. 1). Due to an extreme HLA polymorphism and the fact that different HLA molecules present different peptides, the HLA "ligandome", which comprises HLA-presented peptides, varies considerably between individuals. But even if one pair of humans happens to express an identical set of HLA molecules, immune reactions are still to be expected after transplantation. Such rejection processes take place more slowly and less vigorously than typical alloreactions between HLA-mismatched individuals. They are caused by the presentation of peptides derived from polymorphic non-HLA proteins, whereby the polymorphic spot has found access to HLA-mediated presentation. As a consequence, in a given donor/recipient pair an HLA molecule expressed by both partners may nevertheless present peptides of different sequences from identical regions of the same protein. Thus, reactions leading to graft-versus-host disease are triggered, but leukaemia patients may also benefit from such slight mismatches after stem cell transplantation. Indeed, the graft-versus-leukaemia effect [4] currently represents the most efficient immunotherapy against cancer that is available. For example, the most common HLA molecule in Caucasians, HLA-A*0201, may present either variant of the HA-1 minor histocompatibility antigen (miHAg), VLHDDLLEA or VLRDDLLEA [5–7]. Donors homozygous for the R variant are expected to possess T cells specific for the H variant as part of their T cell repertoire. Thus, the T cell reaction caused by this minor H antigen follows the classical rules of antigen presentation and T cell recognition: Peptides are cleaved from their source protein (usually by the proteasome), transported into the lumen of the endoplasmic reticulum by a peptide transporter called TAP, bound in an allele-specific way by HLA molecules following the rules

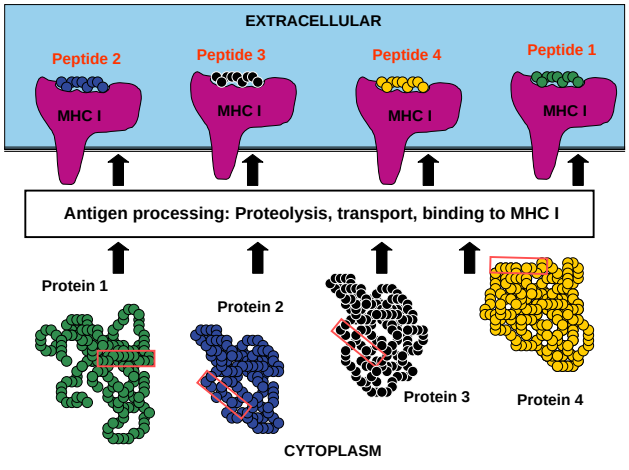

Fig. 1. MHC class I molecules present peptides derived from intracellular proteins at the cell surface.

Table 1
Internet programs for the prediction of antigen processing

Program	Prediction of			Address
	PRO	TAP	MHC	
BIMAS			+	www-bimas.dcrt.nih.gov/molbio/hla_bind
HLA ligand			+	http://hlaligand.ouhsc.edu
MAPPP	+		+	www.mpiib-berlin.mpg.de/MAPPP
MHC-pathway	+	+	+	www.mhc-pathway.net
MHCPred			+	www.jenner.ac.uk/MHCPred
NetChop	+			www.cbs.dtu.dk/services/NetChop
NetMHC			+	www.cbs.dtu.dk/services/NetMHC
PAPROC	+			www.paproc.de
PREDEP			+	http://bioinfo.md.huji.ac.il/marg/Teppred/mhc-bind
ProPred-I	+		+	www.imtech.res.in/raghava/propred1/index.html
RANKPEP	+		+	www.mifoundation.org/Tools/rankpep.html
SVMHC			+	www.sbc.su.se/svmhc/new.cgi
SYFPEITHI			+	www.syfpeithi.de

PRO, proteasomal processing; TAP, transport by the transporter associated with antigen processing; MHC, binding to MHC molecules.

known as "peptide motifs" [8], and finally presented at the cell surface until recognized by a T cell receptor. While we know the sequences of several thousand different HLA-presented peptides, only a small number of such polymorphic HLA-presented peptides have already been identified, most of which can be attributed to Els Goulmy's group in Leiden [9].

3. Antigen processing is predictable

The series of events leading up to the presentation of peptides by MHC molecules is termed "antigen processing". Three major steps contribute to the pathway of MHC class I antigen processing and shape the repertoire of presented peptides: processing by the proteasome, transport by TAP, and binding to nascent MHC molecules (Fig. 1). Prediction programs have been established for these three steps and they are accessible without restriction via the world wide web. Additional steps that contribute to class I processing, for example intracellular transport by chaperones, cytosolic processing by proteases other than the proteasome, and trimming in the lumen of the ER, have not yet been brought under the auspices of bioinformaticians, nor can the proteolytic events leading up to MHC class II ligands be predicted. Table 1 lists internet programs that predict either MHC binding [10–16], TAP transport, proteasomal processing [17–19], or a combination of two or all three events, and that might be helpful in T cell epitope prediction. Two of the algorithms were set up in the previous millenium: BIMAS was the first on the net, its predictions are based on binding studies using synthetic peptides. SYFPEITHI was the next to follow, and here the predictions are based exclusively on the characteristics of