Antigenic Peptide Transporter

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1. INTRODUCTION

The transporter associated with antigen processing (TAP) plays a critical role in the major histocompatibility complex (MHC) class I antigen processing pathway by transporting antigenic peptides from the cytosol to the lumen of the endoplasmic reticulum (ER), where the loading of newly synthesized class I molecules takes place. TAP is a member of the large superfamily of ATP-binding cassette (ABC) transporters which possess a characteristic domain structure and transport a wide variety of substrates across membranes in an ATP-dependent manner (for review see Higgins, 1992). Other well-known transporters from this group include P-glycoprotein, which is associated with multidrug resistance (MDR) (Gros et al., 1986), the cystic fibrosis transductance regulator (Riordan et al., 1989) and the sterile 6 transporter in yeast (STE6), which transports the a-type mating factor across the plasma membrane (Kuchler et al., 1989). Since the discovery of the TAP genes in 1990, much progress has been made toward an understanding of the structure and function of this important transporter. It is not the goal of the present work to provide an exhaustive review of TAP developments to date. An excellent review by Tim Elliott (1997) already exists on this subject. Rather, we would like to present an overview of the molecular biology of TAP in the context of TAP as a drug
target. There is a wealth of information on the substrate specificity of TAP and on the inhibition of TAP by viral proteins. In addition, studies have been initiated using a rational approach toward the design of specific TAP inhibitors based on knowledge of the TAP–peptide interaction. Taken together, the data indicate that TAP has the potential to be a drug target, and in certain instances the inhibition of TAP function may be of therapeutic value, such as in the case of tissue transplantation and autoimmune disease. Peptidomimetics appears to be a promising approach toward the development of specific TAP inhibitors.

2. TAP AND THE MHC CLASS I ANTIGEN PROCESSING PATHWAY

2.1. Introduction

Major histocompatibility complex (MHC) class I molecules present antigenic peptides to CD8+ cytotoxic T lymphocytes (CTL). Recognition of the target cell by CTL initiates a chain of events which ultimately leads to the lysis and death of the target cell. In this way, cells which harbor foreign antigens, i.e., viruses, bacteria, or tumor antigens, can be destroyed by the immune system. The MHC class I antigen processing and presentation pathway therefore plays a major role in the immune response to disease. MHC class I antigens (HLA-A, B, and C in humans, H-2-K, D, and L in mice) are highly polymorphic and each locus contains several alleles, each with its own unique peptide-binding specificity (for review see Bjorkman and Parham, 1990). The class I alleles of a given organism are capable of presenting a wide variety of antigenic peptides derived from endogenous foreign proteins. Class I molecules are expressed as a membrane-bound heavy chain (~45 kDa) associated with a soluble light chain (~12 kDa) called β2-microglobulin (β2m). X-ray crystal structure analysis of the class I heterodimer revealed the existence of a groove in the α-1 and α-2 domains of the heavy chain which contained bound peptide (Bjorkman et al., 1987). Indeed, proper folding of the heterodimer occurs only in the presence of peptide. The optimal size of the peptide for binding to the groove is 8 – 10 amino acids. The primary function of TAP is to supply these peptides to the class I molecules at the site of assembly, i.e., the ER.

The vast majority of the antigenic peptides presented by class I molecules are generated in the cell cytosol. Degradation of the antigens is mediated through the action of the proteasome, a large multicatalytic protease (Goldberg and Rock, 1992; Tanaka et al., 1997), which is the primary mode of protein degradation in the cytosol. Antigens are degraded in a ubiquitin- and ATP-dependent manner. Because the peptides are generated in the cytosol and the site of class I assembly is in the ER, there must be a mechanism for the delivery of the peptides to the ER. The existence of a peptide transporter for this purpose was hypothesized prior to