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REVIEW

Thymoproteasome and peptidic self

Yousuke Takahama[1,2] · Izumi Ohigashi[2] · Shigeo Murata[3] · Keiji Tanaka[4]

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Abstract

Positive selection of T cells in the thymus is induced by low-affinity TCR recognition of self-peptide-MHC complexes expressed by cortical thymic epithelial cells (cTECs). cTECs express a specialized type of proteasomes, the thymoproteasome, which generates a unique spectrum of MHC class I-associated peptides and plays a critical role in thymic positive selection of $CD8^+$ T cells. However, it remains unclear how the thymoproteasome contributes to the thymic positive selection. More than 30 years ago, the "peptidic self" hypothesis proposed that TCRs recognize MHC-presented peptides only, without interacting with MHC molecules, which turned out to be incorrect. Interestingly, however, by implying that a set of MHC-associated peptides forms immunological self, this hypothesis also predicted that positive selection in the thymus is the primary immune response to "foreign epitope" peptides during T cell development. The thymoproteasome-dependent unique self-peptides may create those foreign epitope peptides displayed in the thymus for positive selection of T cells.

Keywords Proteasome · Thymus · Positive selection · Immunological self

Introduction

It has become clear that positive selection of $CD8^+$ T cells in the thymus relies on a unique type of proteasomes, termed the thymoproteasome, which is specifically expressed in cortical thymic epithelial cells (cTECs) (Murata et al. 2007; Tomaru et al. 2009; Ripen et al. 2011; Ohigashi et al. 2013). The thymoproteasome is characterized by its cTEC-specific catalytic component, β5t (also known as PSMB11), which alters the substrate specificity of proteolysis (Murata et al. 2007; Florea et al. 2010; Sasaki et al. 2015). Experiments using β5t-deficient mice, which lack the thymoproteasome, revealed that the thymoproteasome plays essential roles in development of $CD8^+$ T cells by optimizing their cellularity (Murata et al. 2007; Xing et al. 2013; Ohigashi et al. 2013), TCR repertoire (Nitta et al. 2010; Xing et al. 2013), and TCR responsiveness (Takada et al. 2015). Because proteasomes are responsible for the production of the peptides associated with MHC class I molecules and because those peptide-MHC class I complexes are presented to and recognized by $CD8^+$ T cells, it is reasonable to speculate that the thymoproteasome produces a unique set of peptides in cTECs, which display a unique repertoire of MHC class I-associated peptides that potently and efficiently promote positive selection of $CD8^+$ T cells (Murata et al. 2008; Takahama et al. 2010; Klein et al. 2014; Kincaid et al. 2016; Murata et al. 2018). However, the biochemical and structural nature of thymoproteasome-dependent peptides expressed in cTECs has not been elucidated. Consequently, it remains unclear how, and indeed whether, thymoproteasome-dependent peptides contribute to positive selection of $CD8^+$ T cells (Murata et al. 2018).

Several models have been proposed to explain how thymoproteasome-dependent peptides efficiently induce positive selection of $CD8^+$ T cells. One possibility is that the difference between thymoproteasome-dependent peptides and those generated by other forms of proteasomes avoids overlap between MHC class I-associated peptides displayed by cTECs and other antigen-presenting cells ("peptide switch" hypothesis) (Kincaid et al. 2016; Murata et al. 2018). The

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✉ Yousuke Takahama
yousuke.takahama@nih.gov

[1] Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

[2] Institute of Advanced Medical Sciences, University of Tokushima, Tokushima 770-8503, Japan

[3] Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan

[4] Laboratory of Protein Metabolism, Tokyo Metropolitan Institute of Medical Science, Tokyo 156-8506, Japan

difference among the spectra of these peptides opens a window for positively selected T cells to escape from negative selection (Kincaid et al. 2016). Alternatively, thymopro teasome-dependent MHC class I-associated peptides may be structurally enriched in peptides that have epitopes for low-affinity interactions with TCRs ("low affinity motif" hypothesis) (Sasaki et al. 2015; Murata et al. 2018). This view agrees with the notion that low-affinity interactions between peptide-MHC complexes and TCRs would efficiently promote positive selection of T cells (Starr et al. 2003; Takahama et al. 2008). These two possibilities are not mutually exclusive, and both warrant further experimental and conceptual examination. Here, we extend our speculations on the role of thymoproteasome-dependent self-peptides in thymic selection with respect to the "peptidic self" hypothesis, originally described in 1986 (Kourilsky and Claverie 1986).

Peptidic self

Since the proposal of the germ-line specificity hypothesis published in 1971 by Niels Jerne (Jerne 1971), MHC molecules have been considered to play a central role in antigen recognition by T cells and their repertoire selection in the thymus (Katz et al. 1973; Bevan 1977; Zinkernagel et al. 1978; Kisielow et al. 1988). The findings in the mid-80s of protein antigen processing pathways and peptide antigen presentation in association with MHC molecules (Babbitt et al. 1985; Townsend et al. 1986) brought the peptides, both foreign and self, to join MHC molecules on center stage with regard to T cell recognition and selection (Bjorkman et al. 1987; Stern et al. 1994). Indeed, experiments then revealed that MHC-associated peptidic self-antigens in the thymus impact positive selection of T cells (Singer et al. 1986; Nikolic-Zujic and Bevan 1990).

In 1986, Phillipe Kourilsky and Jean-Michel Claverie published their proposal that the set of peptides exposed at the surface of somatic cells represents "somatic self," or peptidic self, and those peptides that do not belong to peptidic self would be recognized as "foreign" (Kourilsky and Claverie 1986). The key body of the hypothesis was that TCRs recognize MHC-presented peptides only, without directly interacting with MHC molecules. In this scenario, TCRs are actually the receptors for the peptides but not MHCs, and TCR recognition appears MHC-restricted because peptide epitopes for the interaction with TCRs are heavily influenced by polymorphic structure of MHC molecules (Kourilsky and Claverie 1986). This basic proposal of the hypothesis turned out to be incorrect, as the crystal structure analysis later demonstrated that TCRs directly interact with both MHC-associated peptides and peptide-associated MHC molecules (Garboczi et al. 1996; Garcia et al. 1998; Reinherz et al. 1999). Nevertheless, Kourilsky and Claverie extended the peptidic self hypothesis to thymic T cell repertoire formation, by proposing that positive selection in the thymus could mean "the primary reactions against real (rather than virtual) peptides taking place during ontogeny of the T cells, particularly in the thymus" (Kourilsky and Claverie 1989). To stimulate this primary reaction, the thymus must display a broad variety of "foreign epitopes," which interact with TCRs expressed by developing thymocytes with a "bona fide high-avidity" interaction (Kourilsky and Claverie 1989). Because the foreign epitope peptides must be presented in association with MHC molecules, it is then "no mystery that mature T cell repertoire bears the imprint of MHC" (Kourilsky and Claverie 1989). Kourilsky and Claverie further extended their hypothesis by addressing that "the next problem is to identify the source of these functionally 'foreign' elements" and suggested that the thymic epithelial cells must "present a large variety of erroneous self peptides," possibly generated by errors in gene expression, in particular, protein translation. Such an "unavoidable noise of errors in gene expression would be a major driving force" for T cell repertoire formation (Kourilsky and Claverie 1989).

Thus, despite the body of the peptidic self hypothesis proposing that TCRs only recognize peptides but not MHCs turned out to be incorrect, the peptidic self hypothesis also highlighted the importance of the MHC-associated "peptidome" in the immune system, including the thymic selection, and proposed that (i) positive selection is the primary immune response to foreign peptides, (ii) positive selection is mediated by high-avidity TCR engagement, and (iii) positive-selection-inducing thymic epithelial cells display foreign peptides by utilizing erroneously translated self-peptides.

Structure of the thymoproteasome

The catalytic core of the enzymatically active proteasome is the 20S proteasome, which consists of four heteroheptameric rings (two outer α rings and two inner β rings) with an $\alpha_{1–7}$ $\beta_{1–7}$ $\beta_{1–7}$ $\alpha_{1–7}$ stoichiometry. The 20S proteasome exposes catalytic threonine residues at the inner surface of the chamber formed by the two abutting β rings, with β1, β2, and β5 exerting caspase-like, trypsin-like, and chymotrypsin-like activities, respectively (Fig. 1a). In jawed vertebrates, these catalytic subunits are diverse to form the proteasome isoforms specialized for adaptive immunity, i.e., the immunoproteasome (β1i, β2i, and β5i) and thymoproteasome (β1i, β2i, and β5t). The quaternary structures of the bovine constitutive proteasome (Unno et al. 2002), as well as mouse and human immunoproteasomes (Huber et al. 2012; Santos et al. 2017), have been reported. The chymotryptic activities of β5 and β5i play a critical role in producing antigenic peptides associated with MHC class I molecules, because the C-terminal hydrophobic residues of the peptides are the main anchors in the peptide-binding groove

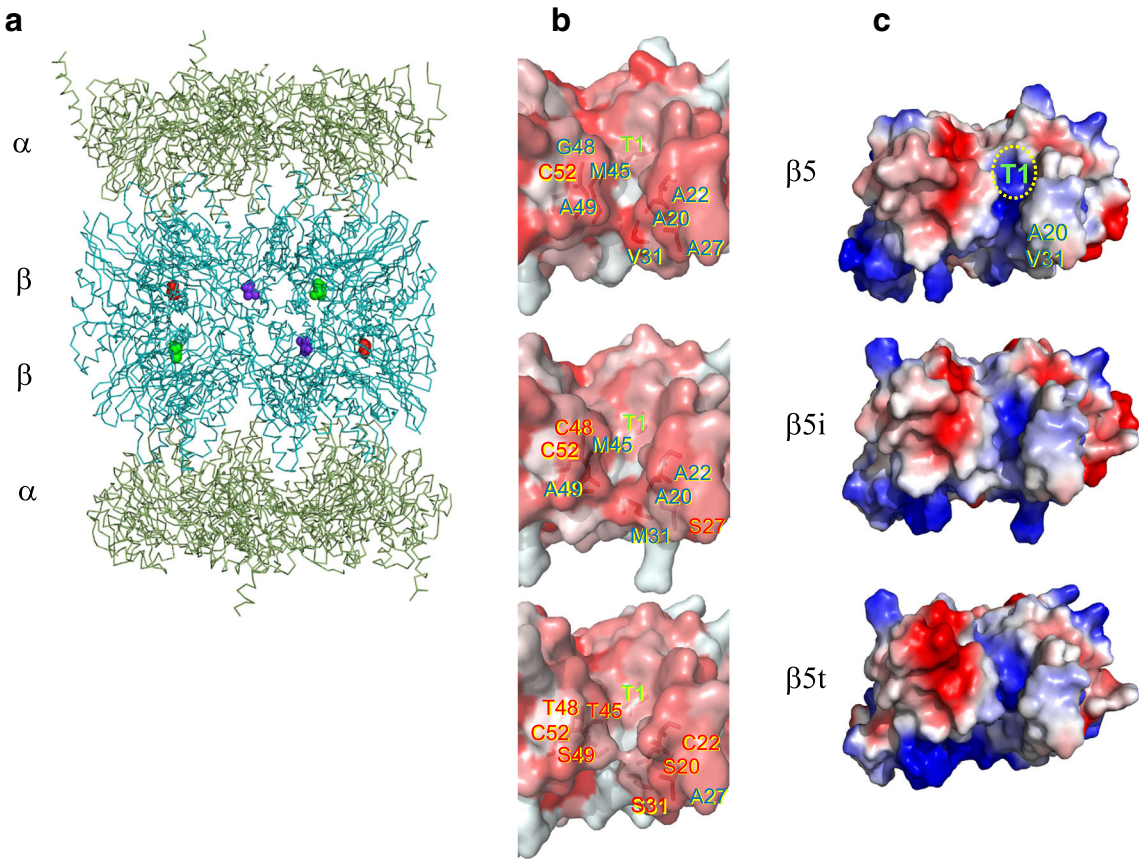

Fig. 1 Structures of β5 family catalytic subunits of the proteasome. **a** Cα representation of the bovine constitutive proteasome (PDB: 1IRU). Active threonine residues of β1, β2, and β5 appear in purple, red, and green, respectively. **b** Diagrams of hydrophobicity of the substrate-binding pockets of the active sites of mouse β5 (top), β5i (middle), and β5t (bottom). The surface is colored according to hydrophobicity (*red,* hydrophobic; *white,* hydrophilic). Hydrophobic and hydrophilic amino acid residues comprising the substrate-binding pocket in mouse β5, β5i, and β5t are indicated in blue and red letters, respectively. T1: catalytic threonine residue (green letter). **c** Diagrams of electrostatic surface potential of the substrate-binding pockets for the active sites of mouse β5 (top), β5i (middle), and β5t (bottom). The surface is colored according to electrostatic potential (*blue,* positive; *red,* negative). The catalytic threonine residue in β5 is surrounded by a dotted circle (top). Residues of the pocket in β5 (A20 and V31) are also highlighted in green letters. The structures of β5 and β5i were adopted from the mouse constitutive proteasome (PDB 1D: 3UNE) and immunoproteasome (PDB 1D: 3UNH), respectively. The structure of β5t was predicted based on that of β5

of MHC class I molecules. The tertiary structure of the three β subunits, including the structure of β5t predicted based on that of β5, suggests that their overall structures resemble one another (amino acid sequence identities between β5 and β5i, 70.6%; β5 and β5t, 54.1%; and β5i and β5t, 42.4%). However, the hydrophobicity and electrostatic surface potential of their substrate-binding pockets are different (Fig. 1b, c), and the primary structure of the substrate pocket of β5t differs remarkably from those of β5 and β5i (Fig. 1b). The pockets of β5 and β5i consist mostly of hydrophobic amino acid residues, which hydrophobic substrates can easily access. By contrast, the substrate-binding pocket of β5t is mainly composed of hydrophilic amino acid residues, suggesting that β5t actually exhibits no or very low chymotrypsin-like activity. Indeed, the immunoproteasome and thymoproteasome exhibit distinct hydrolytic patterns on model protein substrates in vitro (Sasaki et al. 2015), indicating that the thymoproteasome has unique catalytic properties, especially with regard to the production of MHC class I-associated peptides.

Peptidic self and thymoproteasomes

According to the extended part of the peptidic self hypothesis, positive selection represents the bona fide primary response to foreign peptides—a notion that might have been too provocative at the time it was proposed (Kourilsky and Claverie 1989). However, the identification of the thymoproteasome has changed the situation. The thymoproteasome has unique substrate specificity for degradation of cytoplasmic proteins (Murata et al. 2007; Sasaki et al. 2015) and thereby is capable of providing a unique self, i.e., foreign, MHC-associated peptides, or the self-peptides that differ from conventional self-peptides expressed in other parts of the body (Sasaki et al. 2015). Therefore, the thymoproteasome provides the molecular basis by which positive-selection-inducing thymic epithelial cells display foreign self-peptides to $CD8^+$ T cells. The peptidic self hypothesis does not have to rely on cTEC-specific erroneous self-peptides, which have not yet been demonstrated to exist. Owing to the thymoproteasome, the proposition that

positive selection is the primary immune response to foreign peptides has now a realistic basis. Indeed, it is now clear that TCR affinity and thymoproteasome-dependence during positive selection affect subsequent TCR responsiveness in naïve T cells (Mandl et al. 2013; Persaud et al. 2014; Fulton et al. 2015; Takada et al. 2015), similar to the conditional effects of the magnitude and quality in the primary immune responses onto those in the secondary immune responses.

Moreover, the peptidic self hypothesis, which assumes that positive selection is the immune response to foreign peptides, appears compatible with the peptide switch hypothesis for the thymoproteasome dependence of positive selection. The thymoproteasome-dependent foreign self-peptides uniquely displayed by cTECs do not overlap with ordinary self-peptides displayed everywhere else in the body, and this difference between foreign self-peptides and nominal self-peptides creates the peptide switch between positive and negative selection.

Nonetheless, the peptidic self hypothesis that predicts that positive selection is mediated by high-avidity TCR engagement does not seem to fit with our current understanding of the mechanism for positive selection, in which the affinity between TCR and peptide-MHC complex makes a major contribution to the outcome of thymic selection and positive selection is induced by low-affinity TCR recognition of self-peptide-MHC complexes (Starr et al. 2003; Palmer and Naeher 2009; Morris and Allen 2012). The contradiction may also be applied to other predictions about positive selection in the peptidic self hypothesis, because the requirement for high-avidity TCR engagement was the essential basis for the peptidic self hypothesis to predict that positive selection requires TCR interaction with foreign peptides.

However, the current understanding that positive selection demands low-affinity interaction between TCR and peptide-MHC complex is not incompatible with a peptide centric view of the peptidic self hypothesis. On the same line, the "low affinity motif hypothesis" of thymoproteasome dependency in positive selection highlights the role for self-peptides in thymic selection and can thus be compatible with the predictions about thymic repertoire selection in the peptidic self hypothesis. Obviously, the peptide switch hypothesis and the low affinity motif hypothesis for the thymoproteasome-dependent positive selection should be further evaluated.

Additional perspectives on peptidic self and thymic selection

The peptidic self view raises several additional issues worthy of discussion about thymic repertoire selection. As mentioned above, the thymoproteasome liaises the peptidic self with positive selection of $CD8^+$ T cells. The link with positive selection of $CD4^+$ T cells is less clear, although it may involve cathepsin L (CTSL) (Nakagawa et al. 1998; Honey et al. 2002) and the thymus-specific serine protease (TSSP, also known as protease serine 16 or Prss16) (Gommeaux et al. 2009; Viret et al. 2011). CTSL and TSSP are endosomal-lysosomal proteases that are highly expressed in cTECs; however, in contrast to the thymoproteasome, their expression is not clearly cTEC-specific. Via the combination of these two proteases, possibly along with other endosomal-lysosomal proteases, cTECs may display foreign epitope self-peptides associated with MHC class II molecules that are specialized for positive selection of $CD4^+$ T cells.

Promiscuous gene expression by medullary thymic epithelial cells (mTECs) (Klein et al. 1998; Klein and Kyewski 2000) is another interesting feature of the thymus from the standpoint of the peptidic self view of T cell repertoire formation. By promiscuously expressing virtually all of the genes encoded in the genome, the thymic medulla provides almost all self-components present in the body, including tissue-specific self-antigens, thereby contributing to establishment of self-tolerance in newly generated T cells. Thus, the peptidic self displayed by mTECs mirrors the "genomic self" of the organism.

Molecular identification of the MHC-associated peptides displayed by cTECs and mTEC, ae well as by other thymic antigen-presenting cells, is currently a big challenge because of the limited number of these cells isolated from the mouse thymus and the limited sensitivity of MHC-associated peptide analysis by mass spectrometer. However, actual identification of the peptidic self in the thymus will be a giant step towards our understanding of the thymic repertoire formation.

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