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The Development of T-Cell Immunity

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The development of T-cell immunity covers a broad range of possible topics. In this volume, we have attempted to look at four of these topics in detail: the evolution of T-cell immunity, thymic requirements for T-cell immunity, T-cell immunity in the periphery, and prevention of T-cell-dependent autoimmunity. In each section, we have two to three chapters reviewing the latest developments in the field from different perspectives.

The evolution of T-cell immunity was once an area restricted only to speculation. Now with the rise of large-scale "omics" research, the various hypotheses for the origin of T-cell evolution are being rigorously tested. In Chapter 2, Kasahara outlines the genomic innovations that were required for the development of adaptive immunity, in particular T-cell immunity. T-cell immunity is evolutionarily ancient, tracing back to the common ancestor of jawed vertebrates, but adaptive immunity is still more ancient, with an analogous system of lymphocyte-like cells using evolutionarily unrelated and structurally different antigen–receptor systems. The appearance of two analogous systems within a relatively short time period suggests the requirement for a necessary precondition in the common ancestor, which Kasahara suggests may be the freeing up of genetic capacity via several rounds of whole genome duplication. Perhaps worthy of speculation is the idea that the critical importance of the innate immune system prevented excessive experimentation in immunity until redundant copies of the genome became available to allow the evolution of a second immune system layered over the first. In Chapter 3 by Perreault, advances in proteomics data are used to discuss the origin and function of self-peptide presentation on major histocompatibility complex (MHC) class I. Despite the initial assumption of random sampling, recent data indicates that peptide selection is nonrandom, with disproportionate representation from certain classes of proteins. It would be fascinating to know how much of this bias is dictated by biochemical necessity (e.g., easier to process during translation, hence orientation toward rapidly translated proteins) versus an evolutionarily selected bias to increase the efficiency of antiviral defense (i.e., rapidly translated proteins being targeted because they are enriched for viral antigens).

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In the third article of this section Davis and colleagues analyse the evolved complexity of the biochemical recognition between the T cell receptor (TCR) and its cognate antigen. Unlike the B cell receptor, the random rearrangement of TCR genes subsequently requires selection for affinity to the necessary ligand. This creates a tension between random generation of affinity, necessary interaction with self-ligand and yet highly specific and sensitive activation from foreign ligand. While largely unresolved, detailed biochemical analyses of well characterized examples of TCRs suggest potential evolutionary solutions to this conundrum.

T cells are unique in that they need a specialized organ, the thymus, for differentiation. Considered to be only a "lymphocyte graveyard" until the pivotal experiments by Jacques Miller in 1961, the microenvironmental conditions required for T-cell differentiation in the thymus have turned out to be remarkably complex. The two chapters of this section dissect the molecular control over the two sides of T-cell development—the thymocytes themselves and the essential thymic stromal support cells. In Chapter 5, Manley and Condie outline the transcription factor control over early thymic organogenesis, from initial fate specification to end-point differentiation. The authors make the telling point that at this stage a full catalog of the functional subsets of thymic stromal cells is unavailable, leaving a rich field of transcription factor control as yet unexplored. In Chapter 6, Tremblay, Hoang, and Hoang take the novel approach of using the molecular genetics of T-cell acute lymphoblastic leukemia to dissect the thymocyte signaling requirements for survival and differentiation. Together, these chapters show the complexity of the interplay between thymocyte and stroma.

While T-cell immunity is evolutionarily ancient, developing in the common ancestor of all jawed vertebrates, the full collaboration between T cells and B cells is a relatively modern innovation. It is only in eutherian mammals, 125 million years ago, that the sophisticated system of lymph node segregation of function evolved to allow effective T cell help and strong generation of B cell memory. Two chapters in this volume look at the development of the lymph nodes and other secondary lymphoid tissue, which are so important for effective immunity. In Chapter 8, Coles, Kioussis, and Veiga-Fernandes take us through a historical overview of research on secondary lymphoid tissue development, culminating in the conclusions from modern research techniques that have revealed the role of the lymphoid tissue inducer (LTi) cell in creating a structure to bring together CD T cells and B cells in a context to create high-affinity memory responses. In Chapter 7 on this topic, Lane and colleagues look at the role of LTi cells not only in the development of lymph nodes but also in thymic tolerance. They make a convincing argument that the evolution of a powerful CD4 helper T-cell response, complete with CD4 T-cell and B-cell memory and the stimulation of high-affinity antibody production by B cells,

necessitated the coincident evolution of a more stringent mechanism of thymic negative selection. Linterman and Vinuesa follow this theme from the perspective of the key T-cell driver of antibody responses, the follicular T cell (TFH). In Chapter 9, the authors outline the differentiation of the TFH and the role it plays in enabling the germinal center reaction and affinity maturation in B cells. Like Lane and colleagues, Linterman and Vinuesa emphasize the importance of tolerance processes, with an increased risk of autoimmune pathology being the reciprocal cost for the capacity to generate high-affinity antibodies.

The evolution of a high-capacity effector response necessitates the evolution of an efficient suppressive mechanism to prevent catastrophic autoimmunity in the circumstance of the effector response being directed against self-targets. The recessive tolerance mechanisms of negative selection and anergy induction do not provide a fail-safe mechanism against those autoreactive T cells that evade tolerance induction; however, the evolution of dominant tolerance mechanisms ensures efficient suppression of undesirable reactions. In two chapters, one by Romagnoli and van Meerwijk and the other by Kim, the current status of research on the best understood form of dominant tolerance, that of Foxp3^{+} regulatory T cells, is outlined, from differentiation to peripheral function.

In addition to the review chapters outlined above, in this volume we have attempted to display the vibrancy of research in the field of the development of T-cell immunity through commentaries on the data and interpretations in the main reviews. With key breakthroughs occurring in each of the topics presented in this volume, several topics are still highly contentious, with the final models yet to be established.

Genome Duplication and T Cell Immunity

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The adaptive immune system (AIS) mediated by T cells and B cells arose ~ 450 million years ago in a common ancestor of jawed vertebrates. This system was so successful that, once established, it has been maintained in all classes of jawed vertebrates with only minor modifications. One event thought to have contributed to the emergence of this form of AIS is two rounds of whole-genome duplication. This event enabled jawed vertebrate ancestors to acquire many paralogous genes, known as ohnologs, with essential roles in T cell and B cell immunity. Ohnologs encode the key components of the antigen presentation machinery and signal transduction pathway for lymphocyte activation as well as numerous transcription factors important for lymphocyte development. Recently, it has been discovered that jawless vertebrates have developed an AIS employing antigen receptors unrelated to T/B cell receptors, but with marked overall similarities to the AIS of jawed vertebrates. Emerging evidence suggests that a common ancestor of all vertebrates was equipped with T-lymphoid and B-lymphoid lineages.

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I. Introduction

When and how T cell immunity emerged is an important issue in understanding the origin and evolution of the adaptive immune system (AIS). Thanks to the decades-long efforts of immunologists and the advances of genome projects, we now know that the key components of T cell immunity, such as T cell receptors (TCRs) and major histocompatibility complex (MHC) molecules, are present in all classes of jawed vertebrates (gnathostomes) ranging from mammals to the cartilaginous fish, but absent in jawless vertebrates (agnathans) and invertebrates[1–7] (Fig. 1).

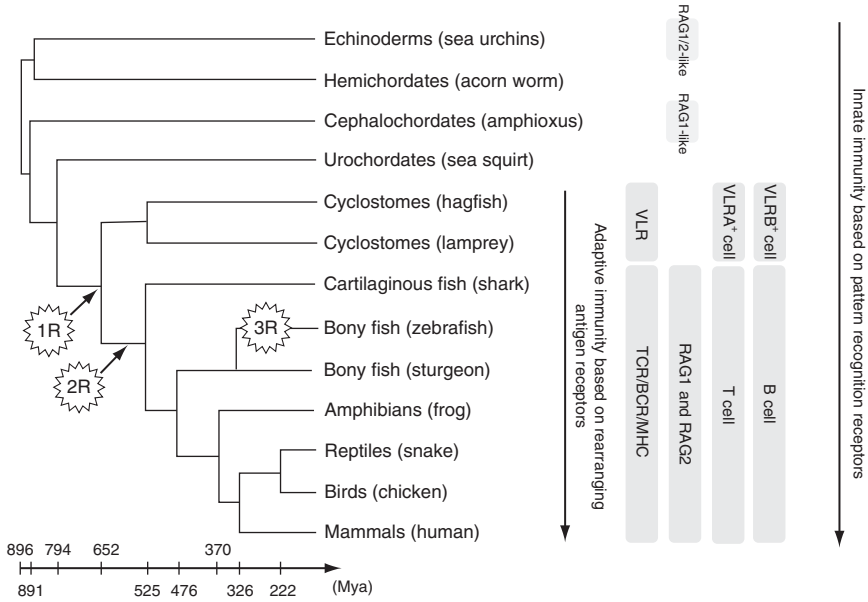

FIG. 1. Evolution of the AIS in deuterostomes. The figure shows schematically at which stage in phylogeny major immune molecules and cells emerged. RAG1-like genes are derived from a transposon; recently, they have been identified also in the genomes of sea urchins[8] and amphioxus.[9] "1R" and "2R" indicate the first and second rounds of WGD. The timing of WGD relative to the emergence of jawless vertebrates is controversial. For detailed discussions, see Section IV and Fig. 4. "3R" stands for a fish-specific WGD. Cephalochordates and urochordates are invertebrate chordates. Cyclostomes, represented by hagfish and lamprey, are jawless vertebrates. Cartilaginous fish, bony fish, amphibians, reptiles, birds, and mammals are jawed vertebrates. The divergence time of animals shown in Mya (million years ago) is based on Blair and Hedges.[12] Abbreviations: BCR, B cell receptor; MHC; major histocompatibility complex; RAG, recombination-activating gene; TCR, T cell receptor; VLR, variable lymphocyte receptor.

Jawless vertebrates represented by hagfish and lamprey are equipped with rearranging antigen receptors that are clonally expressed on lymphocyte-like cells.[13,14] However, their receptors, known as variable lymphocyte receptors (VLRs), generate diversity through somatic recombination of leucine-rich repeat (LRR) modules, and are hence structurally unrelated to TCRs or B cell receptors (BCRs).[15–19] In invertebrate chordates, such as urochordates (represented by sea squirts *Ciona intestinalis*) and cephalochordates (represented by amphioxus *Branchiostoma floridae*), draft genome sequence analysis has provided no evidence for the presence of the AIS.[9,20] Thus, accumulated evidence indicates that T cells as defined by the expression of TCRs are unique to jawed vertebrates and that authentic T cell immunity arose in a common ancestor of jawed vertebrates.

Less well understood is how T cell immunity, and more generally the AIS, emerged in evolution. In terms of molecular components, the cartilaginous fish have fully developed AISs essentially identical to those of mammals; they have not only TCRs of α/β and γ/δ types and BCRs,[2,21,22] but also MHC class I and class II molecules,[23–26] recombination-activating gene (RAG) recombinases,[27] and the components of the classical pathway of complement activation.[28] By sharp contrast, jawless vertebrates have none of these components, giving the impression that the TCR/BCR/MHC-based AIS emerged abruptly in a jawed vertebrate lineage.[3,29,30]

One event widely believed to have contributed to the emergence of the jawed vertebrate-type AIS is the acquisition of RAG recombinases that cut double-stranded DNA at the recombination signal sequence (RSS) and mediate V(D)J recombination in TCR/BCR loci.[31,32] Not only does the site-specific recombination process mediated by RAG share mechanistic similarities with the integration and excision process of transposable elements,[33] but also, RAG proteins can transpose an RSS-containing cleavage product to an unrelated target DNA *in vitro*.[34,35] Furthermore, the DNA-binding region of RAG1 shows sequence similarity to that of a *Transib* superfamily of DNA transposons.[36] Collectively, these observations have provided strong evidence that RAGs originated from transposons. The horizontal transfer of RAG transposons may have taken place multiple times or only once during deuterostome evolution.[8] However, the insertion of RAG transposons in an appropriate context ("appropriate" in the sense that the insertion disrupted an ancestral antigen receptor gene and eventually conferred upon it the ability to rearrange) seems to have taken place only in a common ancestor of jawed vertebrates. Exploitation of RAG transposons as V(D)J recombinases was most likely accidental, thus explaining why combinatorial antigen receptors such as TCRs and BCRs emerged abruptly in jawed vertebrates.

Another event assumed to have played a pivotal role in the emergence of the jawed vertebrate-type AIS is two rounds of whole-genome duplication (2R-WGD) that occurred early in vertebrate evolution.[3,37] The importance of

this event in the evolution of T cell immunity was initially suggested by the observation that many of the genes encoded in the MHC, including those involved in antigen presentation, arose as a result of large-scale chromosomal duplication that presumably took place as part of WGD.[38,39] With the accumulation of genomic data from key vertebrate and invertebrate species, it is becoming increasingly clear that WGD was an important event that enabled the ancestor of jawed vertebrates to evolve highly sophisticated AISs.[7] Here I review the role of WGD in the emergence of the AIS, with particular emphasis on the evolution of T cell immunity. I then review the latest advances in our understanding of the immune system of jawless vertebrates. Surprisingly, the overall design of the agnathan AIS is similar to that of the gnathostome AIS, despite the fact that jawed and jawless vertebrates use completely different antigen receptors.

II. WGD: From a Hypothesis to the Fact

Exactly 40 years ago, Susumu Ohno proposed that the vertebrate genome underwent one or two rounds of WGD at the stage of fish or amphibians through a tetraploidization process.[40] This proposal was based mainly on the comparison of DNA content and karyotypes in various organisms, and the observation that tetraploid species occur naturally in fish and amphibians. Ohno argued that WGDs, which duplicate all genes in the genome simultaneously, were more effective than cumulative tandem duplications in bringing about major evolutionary changes because they would free an entire set of genes from purifying selection and allow it to coevolve, thus providing a unique opportunity to form novel genetic networks required for biologic innovations.

Although his proposal was quite influential from its inception, it was viewed with skepticism until the mid-1990s because of the paucity of experimental evidence. However, with the progress of genome projects, observations supporting Ohno's hypothesis, which became known as the 2R (two-round) hypothesis after some refinement,[41] accumulated exponentially. The major supporting evidence is twofold.[42–45] First, a gene, which occurs only in a single copy in invertebrate chordates such as urochordates and cephalochordates, often has multiple, typically up to four, copies (paralogous copies or paralogs) in jawed vertebrates, indicating that there were waves of gene duplication during the transition from invertebrates to jawed vertebrates. Second, such paralogs, often called ohnologs in honor of Ohno,[46] are not distributed randomly in the vertebrate genome, but tend to occur in clusters (called paralogons) on multiple, and typically four, separate chromosomes.[47] For example, the human genome contains four *HOX* clusters[48] (Fig. 2). Here, not only is the *HOX* gene cluster quadruplicated on four separate chromosomes, but also, many of

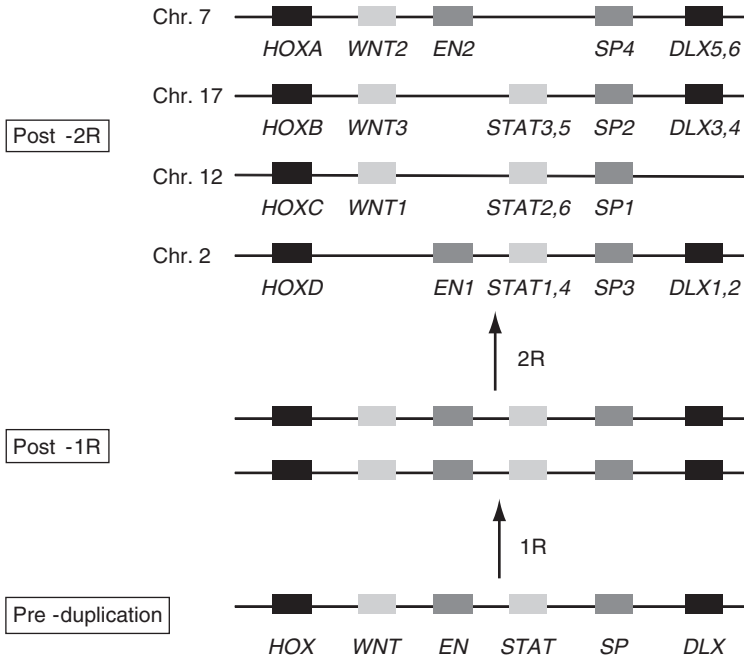

FIG. 2. Origin of the *HOX* paralogy group. Genes are arranged arbitrarily to emphasize corresponding paralogs. The upper panel shows four sets of paralogons constituting the human *HOX* paralogy group. Invertebrate chordates such as amphioxus have only a single *HOX* gene cluster.[49] "1R" and "2R" indicate the first and second rounds of WGD, respectively. Abbreviations: Chr, chromosome; DLX, distal-less homeobox; EN, engrailed homeobox: HOX, homeobox; SP, specificity protein transcription factors; STAT, signal transducer and activator of transcription; WNT, wingless-type MMTV integration site family member.

the genes adjacent to the *HOX* gene cluster are quadruplicated, triplicated, or duplicated on the same four sets of chromosomes, indicating that this unique arrangement of paralogs, known as genome paralogy, arose not as a result of individual gene duplications, but as a consequence of two rounds of large-scale block duplication.

A close inspection of the vertebrate genome indicates that genome paralogy is by no means an exceptional observation. Dehal and Boore[50] systematically identified ohnologs by comparing human and sea squirt genomes and examined their locations in the human genome; their analysis showed that $\sim 25\%$ of the human genome is covered by four sets of paralogons, indicating that genome paralogy is an essential feature of human genome architecture. More recently, comparison of the human and amphioxus genomes revealed widespread occurrence of quadruple conserved synteny, where four sets of human

paralogons corresponded to one set of linked genes in amphioxus.[51] These observations provided incontrovertible evidence for the 2R hypothesis. It is now widely accepted that 2R-WGD took place in the vertebrate lineage after its separation from invertebrate chordates, but before the radiation of jawed vertebrates[41,45,52,53] (Fig. 1). Apart from the 2R-WGD discussed earlier, an ancestor of the majority of ray-finned fish experienced a lineage-specific WGD ~320 million years ago.[11] This duplication is often called 3R (the third round of WGD).

III. Roles of Ohnologs in Adaptive Immunity

The function of the jawed vertebrate-type AIS depends on the participation of a large number of genes. Klein and Nikolaidis[4] have classified the genes deployed by the AIS into three categories. The first category includes genes that evolved long before the emergence of the AIS. Because these genes evolved for other biologic systems and were subsequently recruited to the AIS, they usually have functions not restricted to adaptive immune responses. For example, the proteasome, a proteolytic enzyme complex,[54] evolved as protein degradation machinery essential for cell survival and was later recruited as a supplier of peptides to MHC class I molecules.[55] Thus, most of the proteasome subunits are well conserved throughout eukaryotes, and their functions are not specialized for the AIS.[54]

The second category includes paralogs that emerged by duplication from preexisting genes and acquired functions involved in or specialized for adaptive immune responses. Many of these genes appear to be ohnologs generated by 2R-WGD.[56] For example, jawed vertebrates have a specialized type of proteasomes, called immunoproteasomes, that facilitates the production of peptides that serve as MHC class I ligands.[57,58] Instead of β1, β2, and β5 subunits found in regular proteasomes, immunoproteasomes contain three interferon (IFN)-γ-inducible subunits called β1i, β2i, and β5i.[55] These subunits alter the cleavage specificities of the proteasome so that peptides suitable for binding to MHC class I molecules are produced more efficiently. The genes coding for β1i, β2i, and β5i are related to those coding for β1, β2, and β5 subunits, respectively, and the former set of genes are ohnologs that arose by WGD from the latter set of evolutionarily more ancient genes with housekeeping functions.[55]

The third category includes a relatively small number of genes, such as those coding for MHC class I and class II molecules, TCRs, and BCRs, with functions dedicated to immune responses. These genes appear to have emerged by mechanisms other than simple duplication of preexisting genes; in the case of MHC class I and class II molecules, peptide-binding domains of

unknown origin appear to have been grafted to the immunoglobulin (Ig)-like constant domains.[59,60] In the case of antigen receptors, an invasion by RAG transposons was instrumental in their emergence.[31]

Here, representative examples of ohnologs are discussed to highlight the importance of WGD in the emergence of the jawed vertebrate-type AIS.

A. Molecules of the MHC System

The MHC system is a cornerstone of T cell immunity because conventional α/β TCRs recognize antigen only in the form of peptides bound to MHC class I or class II molecules. Accumulated evidence indicates that many molecules involved in antigen presentation by class I and class II molecules are encoded by ohnologs[7,61] (Table I). Peptides presented by class I molecules are produced by proteasomes and transported to the endoplasmic reticulum by transporters associated with antigen processing (TAP), where they bind to nascent class I molecules with the help of tapasin.[62] Immunoproteasome subunits, β1i, β2i, and β5i, are encoded by ohnologs as discussed earlier, and so are the TAP and tapasin molecules.[7] Recently, a novel form of proteasomes, designated thymoproteasomes, has been identified in mice[63] and man.[64] Thymoproteasomes, expressed specifically in cortical thymic epithelial cells, are involved in positive selection of $CD8^+$ T cells.[65] β5t, a β-type subunit unique to thymoproteasomes, is also encoded by an ohnolog (Table I).

Peptides presented by MHC class II molecules are produced by endosomal/lysosomal proteases. Important among such proteases are cathepsins[66,67]; accumulated evidence indicates that cathepsins S, D, and L play particularly important roles in antigen presentation by class II molecules and that cathepsin L is involved in thymic selection of $CD4^+$ T cells and degradation of invariant chains.[68] As described below, the majority of cathepsin isoforms are encoded by ohnologs mapping to paralogons (Table I). Other examples of ohnologs directly related to the function of MHC molecules are *RXRB* (retinoid X receptor β) and *RFX5* (regulatory factor X, 5) genes, which regulate the expression of class I and class II molecules, respectively.[69,70]

The MHC is a prototypical region exhibiting genome paralogy.[61,71] Initially, the MHC paralogy group was defined as a set of paralogons located on human chromosomes 1, 6, 9, and 19.[37,39] Recent evidence indicates that the MHC paralogy group and the neurotrophin paralogy group[72] are partially overlapping and that they descended from a neighboring region on the same ancestral chromosome[41,73] (Fig. 3). It is remarkable that almost all of the ohnologs discussed earlier are located in the paralogons of the MHC/neurotrophin paralogy group.[7] This suggests that a preduplicated region that existed in the genome of our invertebrate chordate ancestor contained precursors of many genes coding for the components of the MHC system.[71,75]

TABLE I
REPRESENTATIVE HUMAN OHNOLOGS INVOLVED IN ANTIGEN PRESENTATION

Gene family	Genes	Location[a]	Gene products	Function	Other closely related ohnologs	Location[a]
Ohnologs involved in class I antigen presentation						
20S proteasome	*PSMB8*	6p21.3 (MHC)	β5i	Component of immunoproteasomes: production of MHC class I-binding peptides	*PSMB5*	14q11.2
β-subunits	*PSMB9*	6p21.3 (MHC)	β1i	Component of immunoproteasomes: production of MHC class I-binding peptides	*PSMB6*	17p13
	PSMB10	16q22.1	β2i	Component of immunoproteasomes: production of MHC class I-binding peptides	*PSMB7*	9q34.11–q34.12
	PSMB11	14q11.2	β5t	Component of thymoproteasomes: positive selection of $CD8^+$ T cells		
TAP	*TAP1*	6p21.3 (MHC)	TAP1	TAP1/TAP2 heterodimer transports peptides into the endoplasmic reticulum	*ABCB9 (TAPL)*	12q24
	TAP2	6p21.3 (MHC)	TAP2			
Tapasin	*TAPBP*	6p21.3 (MHC)	Tapasin	Promotes association of TAP and MHC class I molecules	*TAPBPL*	12p13.3
Retinoid X receptor	*RXRB*	6p21.3 (MHC)	RXRβ	Binds to the MHC class I promoter and regulates class I expression	*RXRA* *RXRG*	9q34.3 1q22–q23

Ohnologs involved in class II antigen presentation						
Cathepsins	*CTSL1*	9q21–q22	Cathepsin L1	$CD4^+$ T cell and NKT cell development	*CTSH*	15q24–q25
	CTSL2	9q22.2	Cathepsin L2	$CD4^+$ T cell and NKT cell development	*CTSK*	1q21
	CTSS	1q21	Cathepsin S	Removal of invariant chains in B cells and dendritic cells	*CTSG*	14q11.2
	CTSD	11p15.5	Cathepsin D	Production of MHC class II-binding peptides	*CTSC*	11q14.1–q14.3
					CTSF	11q13.1
					CTSW	11q13.1
Regulatory factor X	*RFX5*	1q21	RFX5	A component of RFX involved in MHC class II expression	*RFX1*	19p13.1
					RFX2	19p13.3–p13.2
					RFX3	9p24.2
					RFX4	12q24

[a]Chromosomal localization of human genes is based on the OMIM database (http://www.ncbi.nlm.nih.gov/omim) or Entrez gene (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene).