approaches the quantum critical point, Tanatar *et al*. could literally "turn off" the Wiedemann-Franz law.

This failure of the Wiedemann-Franz law indicates a severe departure from our standard model of electricity at a quantum critical point. What is going on? Tanatar *et al.* propose an explanation inspired by high-temperature superconductors, in which x-ray measurements show that a continuous Fermi surface breaks up contiguous regions, separated by dead zones where well-defined electrons cease to exist (*10*). Tanatar *et al*. propose that at the quantum critical point, the Fermi surface of $CeCoIn_5$ breaks up into an annulus (see the right panel of the figure), supporting conventional charge and heat transport parallel to the planes of the crystal. But we still do not know what replaces the electron in the directions where the Wiedemann-Franz law fails.

It has taken more than 100 years to find a chink in the armor of the Wiedemann-Franz law, and this new discovery may herald a new understanding of how electricity can transform itself under extreme conditions. Some have suggested that in the fluctuating environment of quantum criticality, the electron actually breaks up into different components (*5*, *11*); it may even break up into separate spin and charge excitations (*12*, *13*). The idea that the electrons may break up into two different groups has also been advanced (*14*), but it is fair to say that no one anticipated this fascinating anisotropic separation into two components. Tanatar *et al.* can rule out some of these scenarios, but certainly not all. What is clear, however, is that at the quantum critical point, a new kind of electricity takes over, and we are only just beginning to understand its properties.

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IMMUNOLOGY

# The Cutting Edge of T Cell Selection

The selection of T cells requires their exposure to a repertoire of peptides generated by an organelle whose structure is thymus-specific.

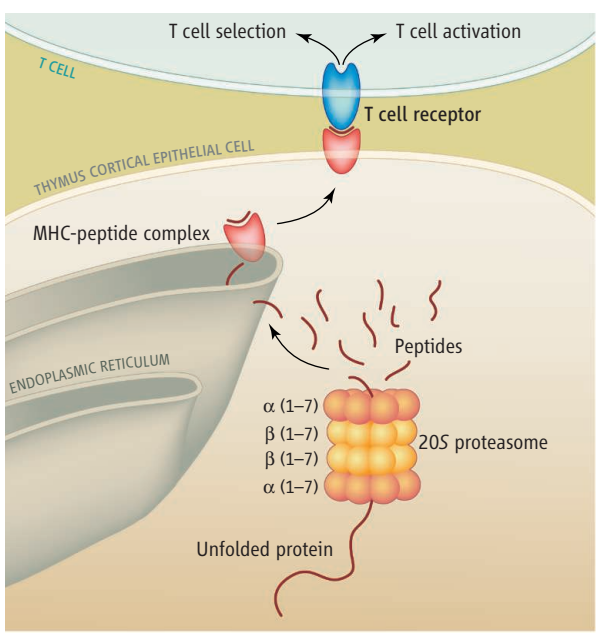
**Michael J. Bevan**

Why should a single cell type in a single organ of the body express a unique enzymatic component of a protein structure that is ubiquitously expressed? This is the puzzle posed by the study of Murata *et al.* on page 1349 of this issue (*1*), which shows that specific cells in the mouse thymus incorporate a distinct enzyme into their 20*S* proteasomes, the multicatalytic machine that degrades intracellular proteins to peptides. The answer to the puzzle lies in the special role played by these thymic cells in immune system development—that is, determining which immature T cells are selected to survive and populate peripheral lymphoid organs (spleen and lymph nodes), where they survey for unwanted pathogens and tumor cells.

The 20*S* proteasome is a barrel-shaped organelle composed of 14 different proteins in four stacks in the arrangement α(1–7)β(1–7)β(1–7)α(1–7) (see the figure). Misfolded polypeptides in the cell interior are fed into the central bore of the proteasome, where three proteolytic components (β1, β2, and β5) cut them to pieces. The peptides pass out of the proteasome and transit into the endoplasmic reticulum, where a subset binds to the groove of nascent molecules called major histocompatibility (MHC) class I. The MHC-peptide complex folds into a mature structure that is transported to the cell surface, where the MHC molecule "presents" the peptide extracellularly. This process happens in all vertebrate cells, and in humans it is the means by which specific T cells ($CD8^+$ subtype) detect foreign antigens such as those encoded by a virus or by mutated self proteins.

MHC class I genes are enormously polymorphic, and each class I molecule has its own preferred peptide-binding motif to accommodate a different range of peptides 8 to 10 amino acids long (the polymorphism guards against a pathogen evolving away from producing sequences that bind MHC) (*2*). To ensure a best fit of the T cell receptor repertoire with foreign antigens outside the thymus, T cells within the thymus that bear receptors with low-binding affinity for one's own peptides (in the context of an MHC complex) are selected to survive. MHC class I molecules on the surface of thymus cortical epithelial cells select the $CD8^+$ T cell repertoire, whereas MHC class II molecules select the $CD4^+$ T cell repertoire (*3*).

Variation in the makeup and proteolytic specificity of thymus proteasomes has been noted previously (*4*). Murata *et al.* discovered a




**A degradation machine of its own.** Proteasomes in the thymus contain a unique component that alters their proteolytic activity. This allows a range of peptides (bound to MHC molecules) to be expressed at the cell surface and function in T cell selection.

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new catalytic proteasome subunit, designated β5t, expressed exclusively in mouse thymus cortical epithelial cells. It replaces the usual enzymatic component, with a resultant change in proteolytic specificity. In the "thymoproteasome," the chymotrypsin-like activity, which leaves hydrophobic residues at the C terminus of peptides, is dramatically reduced.

The peptide-binding motifs of many MHC class I molecules prefer a hydrophobic residue at the C terminus of bound peptides, raising the suspicion that the thymoproteasome may provide fewer peptides that fit snugly in class I grooves. The authors deleted the β5t-encoding gene in mice and found that although thymus architecture was normal and the development of $CD4^+$ T cells was not diminished, the number of mature $CD8^+$ T cells selected in the thymus decreased by 80%. Thus, the novel β5t component of the thymoproteasome enhances the selection of class I–restricted $CD8^+$ T cells. One obvious explanation for this result is that by decreasing the number of peptides with a hydrophobic C terminus, nascent MHC class I molecules become starved of snug-fitting peptides that stabilize the molecule for cell surface expression. This does not appear to be the case, however, because the expression level of class I molecules on the surface of normal and β5t-deficient epithelial cells is the same.

These new findings on proteasome specificity, MHC class I, and $CD8^+$ T cells are reminiscent of a previous analysis of lysosomal proteases and their effect on the selection of MHC class II–restricted $CD4^+$ T cells in the thymus (*5*). Most peripheral cells that express class II molecules use the enzyme cathepsin S, present in lysosomes, to assist in peptide presentation. In contrast, thymus cortical epithelial cells use lysosomal cathepsin L in place of cathepsin S. Deletion of the cathepsin L-encoding gene in mice reduced the efficiency of $CD4^+$ T cell selection without decreasing the overall level of class II molecule expression. In both cases—proteasomes, MHC class I, and $CD8^+$ T cells and the case of lysosomal proteases, MHC class II, and $CD4^+$ T cells—different cargoes of self peptides presented by MHC molecules in the thymus have a substantial impact on the selection of mature T cells.

The T cell receptor repertoire is not only molded by positive selection on MHC molecules presenting self peptides in the thymus, it is also subjected to negative selection to delete T cells with an affinity for self peptides that is high enough to potentially cause harmful autoimmune reactivity. It is assumed that low-affinity interaction between thymic epithelial cells bearing MHC–self peptide complexes and T cell receptors is required to positively select T cells for maturation, whereas an interaction with a high affinity leads to T cell deletion. In line with this, a number of MHC-peptide complexes have been defined that, on the basis of their affinity for the T cell receptor, can positively select but not delete T cells (*6*, *7*). It has been assumed that a T cell receptor repertoire with "not too high, not too low" affinity for self peptides can be selected without special rules for the peptides responsible for positive selection. However, if the thymus cortical epithelium expresses a unique range of self peptides as Murata *et al.* suggest, this raises the possibility that positive selection may be mediated by self antigens that are not seen outside the thymus (*8*). Such sequestration of the positively selecting peptide may provide a greater safety window between high and low affinity to better guard against activated T cells cross-reacting on self antigens and causing autoimmunity.

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ANTHROPOLOGY

# Walking on Trees

Observations of modern orangutans suggest that human bipedalism may have evolved in the trees rather than on the ground.

**Paul O'Higgins and Sarah Elton**

For decades, researchers have viewed standing upright and walking on the ground on two legs as defining features of the hominins (humans and our closest extinct relatives). However, we are beginning to learn that some apes in the Miocene (5 to 23 million years ago) not only had upright postures (*1*) but also incorporated bipedalism into their motion (*2*, *3*). Such movement may well have occurred in the trees. This raises the possibility that preadaptations for hominin bipedalism arose in arboreal settings rather than in terrestrial environments. On page 1328 of this issue, Thorpe and colleagues present compelling new evidence in support of this theory (*4*). Using observational data from modern orangutans, they argue that hominin bipedal walking is not novel but rather a development of locomotor behaviors already established in the ancestor of great apes.

In modern orangutans, hand-assisted bipedalism with extended lower limbs in the small branches of the forest canopy allows movement on slender, springy supports. This enables the orangutans to access resources in the forest canopy that would otherwise be difficult to procure, or to cross between trees with minimum energy expenditure. These advantages might well have provided sufficient selective pressure for bipedal adaptations in arboreal habitats.

The orangutan model provides three scenarios for the emergence of modern great ape and human locomotor strategies from hand-assisted, straight-lower-limbed, arboreal bipedalism (see the figure). In the first, forest canopy fragmentation during the Miocene of Africa led to increased vertical climbing, rather than always crossing from tree to tree at canopy level. Thorpe *et al.* suggest that this climbing behavior, which is similar to knuckle walking, predisposed gorilla and chimpanzee ancestors to the independent acquisition of forms of knuckle walking. In the second scenario, orangutan ancestors in Southeast Asia became even more specialized in traversing, at canopy level, the shrinking closed-canopy forest. Finally, hominins retained and further adapted preexisting arboreal bipedalism to exploit emerging, more open terrain between forested areas. This third scenario is consistent with the long forelimbs that are found in association with obviously bipedally adapted hindlimbs in various early hominins.

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