and may have a similar effect on the maternal allele of *FWA*. A study reported in a recent issue of *Developmental Cell* (*15*) proposes that imprinting of *MEDEA* is controlled by antagonism between the two DNA-modifying enzymes, MET1 and DEMETER (*15*). Thus, imprinting of *MEDEA* and *FWA* in endosperm may rely on the same mechanism. Initially, both parental copies are silenced, then DEMETER removes methylation of *FWA* 5′ repeats but only for the maternal allele of the central cell, triggering endosperm-specific expression of *FWA*. Unlike *FWA*, which is expressed only during formation of the female gametes, *MEDEA* is expressed during the vegetative phase of the plant life cycle (*16*). It is not yet clear when and how *MEDEA* expression is silenced before female gametogenesis begins. Mutation of *MEDEA* causes a marked phenotype in endosperm (*17*), but only when the mutation is maternally inherited. The maternal effect is currently presumed to rely on the imprinted, silenced status of the paternal allele. In contrast to *MEDEA*, the function of *FWA* in endosperm remains unknown (*18*).

Imprinting in *Arabidopsis* apparently relies on a different mechanism for controlling DNA methylation compared with imprinting in mammals. Imprinting in mammals is linked to DNA methylation of large (up to 100 kb) specific intergenic regions, called imprinting control centers (ICRs), that regulate the expression of a group of genes (*19*). Mammalian DNA methylation undergoes a cycle where it is removed globally in the germline. Imprints are erased in primordial germ cells and are then reestablished during gametogenesis. In plants, no such global demethylation has been detected during the plant life cycle (*20*). Imprinting results from the removal of the methylation mark from one of the parental alleles. Unlike the situation in mammals, the imprinted status of plants is not inherited and appears to be confined to the endosperm, which does not contribute to the next generation.

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IMMUNOLOGY

The Robin Hood of Antigen Presentation

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T lymphocytes recognize a wide variety of antigens including peptides, glycolipids, and phosphorylated metabolites. The diversity of this antigenic repertoire, analogous to that of B lymphocytes, has been appreciated only recently. On pages 523 and 527 of this issue, two reports provide new information about how lipid antigens are presented to and activate T cells (*1*, *2*). In their study, Zhou *et al.* (*1*) reveal how lipid antigens are processed inside antigen-presenting cells before presentation to T cells. In complementary work, Moody *et al.* (*2*) identify lipopeptides as a new class of mycobacterial antigens that activate T cells and may be important in host defense.

Lipids, like peptides, are T cell immunogens if they fulfill three important prerequisites: (i) They must efficiently bind to the appropriate antigen-presenting molecule; (ii) they must form complexes with the presenting molecule that persist long enough to interact with the T cell receptors of a specific T cell population; and (iii) they must be efficiently loaded onto the presenting molecule at low concentrations.

Regarding the first requirement, glycolipid antigens bind via their hydrophobic regions to antigen-presenting molecules of the CD1 family. Resolving the structures of CD1d, CD1b, and CD1a has revealed the structural constraints of CD1 binding to lipid antigens (*3*–*5*). CD1 molecules contain a deep hydrophobic pocket responsible for binding the acyl chains of glycolipid antigens. The hydrophobic pockets of CD1d, CD1a, and CD1b have different shapes, conferring unique lipid-binding capacities.

The second requirement, the prolonged persistence of CD1-glycolipid complexes, is necessary if glycolipids are to be efficient T cell immunogens. Although the half-life of CD1-glycolipid complexes in vivo is unknown, the half-life in living cells in vitro is about 24 hours or longer and varies according to which CD1 molecule is involved (*6*). This period is sufficient to allow interaction of the glycolipid antigen with specific T lymphocytes.

The last requirement, the way in which glycolipid antigens are loaded onto CD1 molecules, is still poorly defined. The Zhou *et al.* work now reveals that endosomal lipid transfer proteins (LTPs) including saposins and GM2-activator proteins are important for loading glycolipid antigens onto CD1d molecules in late endosomes (see the figure). Their study initiates a new chapter in the field of antigen presentation to T cells.

Saposins comprise four different proteins that are found predominantly in the late endosomes of antigen-presenting cells and behave as lipid chaperones (*7*, *8*). They are able to pull glycosphingolipids such as gangliosides out of the endosomal membrane and offer them to hydrolases, which initiate glycolipid degradation. Zhou *et al.* convincingly show that saposins are required for loading recombinant CD1d with sulfatides and phosphatidylserine, two types of self-lipid antigens that are generated inside cells. Saposins optimally execute this function at pH 5.0 (the pH of late endosomes) and at 37°C. Lipid transfer occurs at equimolar ratios of CD1d and saposin, suggesting a direct intermolecular interaction rather than an enzyme-like mechanism.

On the basis of these results, the authors suggest a tug-of-war model in which LTPs and CD1d bind to and thus compete for the same lipid antigen. In this model, LTPs are envisaged as pulling glycolipid antigens from the membranes of late endosomes in antigen-presenting cells, as well as from endosomal CD1d molecules (see the figure). This renders endosomal

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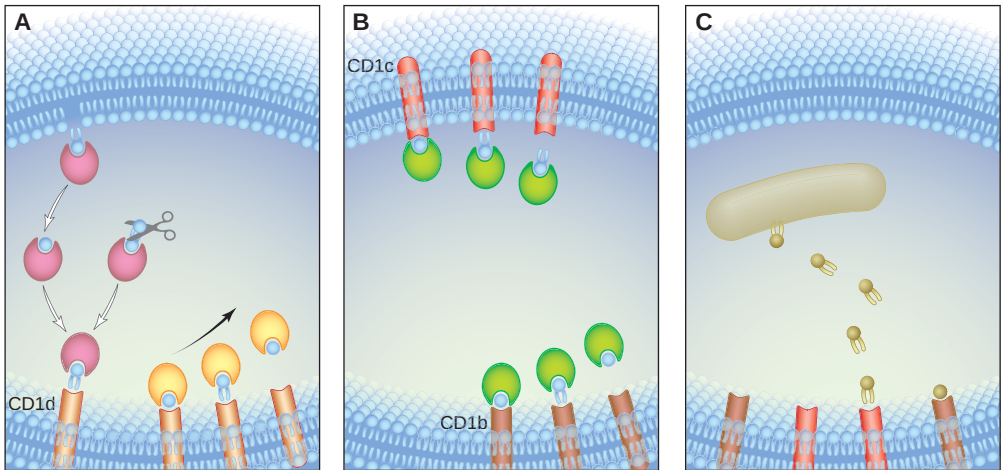
CD1d free to bind to new glycolipid antigen in the endosomal compartment; CD1d then moves to the plasma membrane where it presents its bound antigen to specific T cells. The final outcome is a continuous exchange of lipids between CD1d and LTPs. This model has an important implication: If LTPs bind efficiently to self-lipid antigens, and not to bacterial glycolipid antigens, they would preferentially deprive CD1d of self-lipid antigens, thus facilitating the persistence of complexes of CD1 and microbial glycolipids.

A closer look at the Zhou *et al.* study reveals that saposins are also involved in the processing of glycolipid antigens. Indeed, saposin-deficient antigen-presenting cells cannot activate CD1d-restricted T cells when treated with a digalactosylceramide antigen. This glycolipid requires processing in endosomes by α-glycosidase A before it can stimulate T cells (*9*). With their capacity to offer glycolipids to hydrolases, saposins may directly influence the generation of small, immunogenic glycolipids in endosomes, thus participating directly in the processing of this class of antigen. An important question that remains to be answered is whether LTPs also assist in the binding of lipid antigens to CD1 molecules other than CD1d. Given the binding characteristics of the other CD1 molecules, this is very likely. In that case, LTPs would play a more general part in presenting lipid antigens to T cells.

Zhou *et al.* also show that a deficiency in saposins prevents in vivo expansion of CD1d-restricted T cells belonging to the natural killer T cell population expressing a semi-invariant T cell receptor (iNKT). Such iNKT cells from saposin-deficient mice do not mature in the thymus or expand in the periphery, despite the normal surface expression of CD1d by antigen-presenting cells. A possible explanation for this defect is that CD1d does not present endogenous lipid antigens that stimulate and induce expansion of iNKT cells. This might be a direct consequence of the saposin deficiency, which would prevent CD1d from being loaded with these antigens. This possibility is supported by the finding that saposin-deficient thymus T cells do not stimulate iNKT cells, despite normal expression of surface CD1d. A direct implication is that the lipid antigens stimulating iNKT cells are also recognized by saposins. This information may facilitate the identification of the still unknown self-glycolipids that stimulate iNKT cells.



A tug-of-war for lipid antigens. LTPs exchange lipid antigens with CD1 molecules inside the late endosomes of antigen-presenting cells. (**A**) A saposin LTP (violet) pulls a lipid from the luminal membrane of a late endosome and delivers it to endosomal CD1d (gold). Another saposin LTP (yellow) removes a lipid from endosomal CD1d, freeing up this CD1d molecule so that it can bind to a new lipid antigen. Saposin LTPs may facilitate hydrolase-mediated processing of glycolipid antigens (scissors) by delivering the glycolipid to the hydrolase. (**B**) LTPs (green) may participate in the exchange of lipid antigens bound to CD1b (brown) and CD1c (red), which, like CD1d, are recycled through the late endosomal compartment. (**C**) Glycolipids shed by phagocytosed microbes (beige) do not efficiently bind to LTPs; instead, they form complexes with CD1 molecules that persist longer than complexes between CD1 and self-glycolipids. The functions depicted in (B) and (C) deserve experimental confirmation.

In a complementary study, Moody *et al.* (*2*) report that a family of mycobacterial lipopeptides, called mycobactins, stimulate specific T cell populations. This work shows for the first time that in addition to peptides and glycolipids, lipopeptides are also immunogenic for T cells. This immunogenicity is achieved by binding of the mycobactin lipopeptide through its acyl chain to the CD1a antigen-presenting molecule. This arrangement renders the hydrophilic peptide region of the lipopeptide available for T cell recognition. Mycobactins are presented, at least in this reported case, by CD1a. Mycobactin antigens are likely to be released by mycobacteria within phagosomes and so would need to move to early recycling endosomes where CD1a is located, if they are to be presented on the antigen-presenting cell surface. The intracellular transport mechanisms governing the CD1-restricted presentation of immunogenic lipopeptides remain to be clarified. These transport mechanisms are likely different from those involved in transport into the endoplasmic reticulum and responsible for presentation by major histocompatibility complex class I molecules (*10*).

In addition to mycobactins, it is conceivable that other microbial and self lipoproteins are recognized by T cells. Lipoproteins, like glycolipids, are immunogenic only when bound to CD1 molecules. However, lipoproteins are definitely too big to fit between the CD1 molecule and the T cell receptor (*11*, *12*). Thus, it is possible that they could become immunogenic after an initial processing step that generates smaller lipopeptides. It will be important to investigate the identity of the actors in these processing events, which are likely to include proteases and LTPs. Perhaps saposins or other LTPs might also be involved in the presentation of lipopeptides.

Saposins and other LTPs sort out and redistribute lipid antigens, thus recalling Robin Hood and his band of Merry Men who became legendary for taking and redistributing precious cargo. The two new studies suggest that LTPs and their precious cargo of lipid antigens may become famous as well.

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