to its metabolic nature and low time resolution [6].

The work of Calder *et al.* [8] forms part of an increasing set of evidence which suggests that cortical circuits involved in the encoding of faces are arranged as hierarchical specialized modules. Nevertheless, assuming that the 'modular problem' of face recognition is close to being solved, this can be definitely considered an error. To fully understand this hierarchical organization we need to gain a better understanding about the neural encoding mechanisms. As has been shown by the analysis of populations of neurons recorded in the inferior temporal cortex of monkeys, neurons could show similar tuning properties in multidimensional spaces that do not necessarily reflect the physical properties of the face features but rather other types of information, such as diagnostic information [16] and the familiarity [17] or relevance [18] of the facial features. Work combining different methods and focusing on the neural population and the interactions between different regions will definitely be crucial to understand the level of specificity of the elements involved in the face-recognition machinery.

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Drosophila Immunity: Is Antigen Processing the First Step?

A new genetic study has shown that the phagocytic ability of *Drosophila* blood cells, the hemocytes, may be important for the further induction of an antibacterial response in other tissues.

Dan Hultmark and Karin Borge-Renberg

Though small in size, the fruit fly is no longer considered a flyweight in immunity and it has recently become a pet model for the innate immune response. As with many other insects, infection of flies with bacteria or fungi results in the production of a battery of antimicrobial peptides [1], and these are secreted into the blood from an organ called the fat body. The study of this response has given important insights into the mechanisms of NF-κB activation and the role of Toll and Toll-like receptors in triggering innate immune reactions in other organisms, including man [2–5]. Data from Brennan *et al.* [6], reported in this issue of *Current Biology*, now suggest that the analogy can be taken further.

In insects as well as mammals, the NF-κB family of transcription factors plays a central role in the control of immunity. Two members of the family, Dif and Relish, induce the transcription of antimicrobial peptides, such as cecropin, diptericin and defensin, in the fat body of *Drosophila*. Dif and Relish are the targets of two separate signaling pathways: Dif is activated by signaling from the membrane receptor Toll and Relish by a second receptor, the peptidoglycan recognition protein PGRP-LC, via the so-called Imd pathway [2–5]. Both the Toll and Imd pathways are triggered by peptidoglycans, which are major constituents of bacterial cell walls, and probably by other microbial substances as well [7,8].

It has long been a mystery how fat body cells, which are hidden under a layer of extracellular

matrix, can sense the presence of bacteria. For Toll signaling, part of the explanation may be that the activation is indirect, via a diffusible cytokine called Spätzle. The active form of Spätzle is generated in a proteolytic reaction that depends on several soluble and circulating receptors, including the peptidoglycan recognition protein PGRP-SA [9]. Still, it is not clear how the soluble receptors come into contact with the bacterial peptidoglycans, which are not always accessible on the bacterial surface: in Gram-positive bacteria peptidoglycans are covered by teichoic acids or other surface structures, and in Gram-negative bacteria they are protected by an outer membrane. The access to microbial substances is even more problematic for the Imd signaling pathway, which depends solely on a membrane-localized peptidoglycan receptor, PGRP-LC.

An attractive idea that may resolve this spatial problem is that the initial contact with invading bacteria is not made by the fat body cells but by the hemocytes, macrophage-like cells that patrol the *Drosophila* hemocoel and phagocytose foreign particles, including bacteria. The induction of the response in the fat body would then be indirect and mediated by activated hemocytes. Early attempts to test this idea were disappointing: the *Drosophila* mutants *l(3)hem* and *domino* have few, if any, hemocytes, but they are still able to respond vigorously to injected bacteria [10,11]. However, later experiments with the same mutants showed that, under certain conditions, such as a gut infection with *Erwinia carotovora*, the hemocytes are indeed required for a full response by the fat body [12,13].

Now Brennan *et al.* [6] have discovered a possible link between the phagocytic activity of the hemocytes and the activation of the humoral immune response by the fat body. This group has identified a gene, dubbed *psidin*, which is required for a normal response of the fat body. In particular, the induction of one antibacterial peptide, defensin, is severely affected in *psidin* mutants.

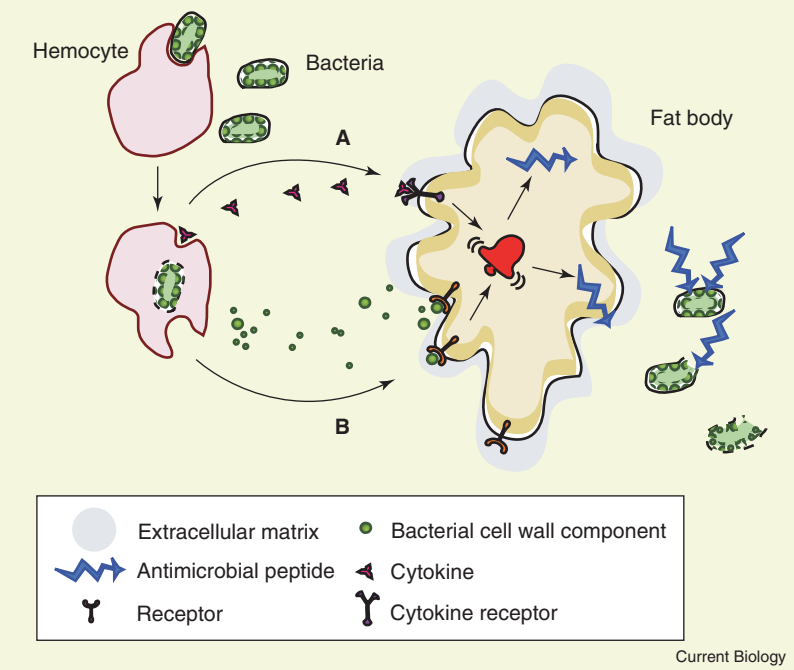

Figure 1. Possible mechanisms for hemocyte-mediated activation of an immune response in the fat body.

Intact bacteria do not interact efficiently with microbial receptors on the fat body, but they are recognized and ingested by circulating hemocytes. Cell wall components from digested bacteria are released in the lysosomal compartment and they may either (A) elicit the production of cytokines that activate the fat body, or (B) become exported from the hemocytes and interact directly with activating receptors on the fat body.

Unlike other genes that affect the antibacterial response, *psidin* is required only in hemocytes, not in the fat body itself. Interestingly, the *psidin* mutant also shows a second phenotype in that its hemocytes fail to lyse phagocytosed bacteria. The protein encoded by the *psidin* gene is associated with lysosomes in *Drosophila* hemocytes and it may play a direct role in the function of these organelles. The induction of defensin is also reduced in the *eater* mutant, which lacks a phagocytosis receptor, providing independent support for a link between phagocytosis and the humoral immune response. However, the effect of *eater* is not as strong as that of *psidin*, perhaps because of a redundancy among phagocytosis receptors.

Although the final proof that the two phenotypes are causally linked must await further experiments, it is an attractive possibility that the bacteria must first be digested in order to make peptidoglycans and other bacterial ligands accessible to the receptors of the innate immune system. Such receptors may even be present in the hemocyte lysosomes, much like TLR9 and other Toll-like receptors in human macrophages [14].

Now the critical question is how the phagocytosis of bacteria by hemocytes leads to activation of fat body and a full-blown humoral response. As the hemocytes are themselves immunoresponsive cells, with functional Toll and Imd signaling systems, it is possible that they are induced to produce cytokines that in turn activate the fat body (Figure 1, pathway A). Brennan *et al.* [6] show that neither the Toll ligand Spätzle nor the JAK/STAT-activating ligand Upd3 are likely to be involved, but other cytokine-like factors may exist. Another possibility is that the hemocytes re-export fragments of the digested bacteria, and that the fat body cells respond to the presence of such fragments (Figure 1, pathway B). Such a model was suggested by Dunn *et al.* [15], who showed that peptidoglycan digestion products elicit a strong immune response in fat body explants from another

insect, the tobacco hornworm *Manduca sexta*. Further support comes from Taniai *et al.* [16], who found that hemocytes from the silkworm, *Bombyx mori*, release lipopolysaccharides from phagocytosed bacteria, and that the presence of such bacterial components correlates with an increased immunostimulatory activity of a hemocyte supernatant.

The latter model predicts that the hemocytes have an efficient mechanism for the export of digestion products, such as peptidoglycan fragments, from phagocytosed microorganisms. That would be an interesting parallel to the antigen-presenting cells of the acquired immune system in vertebrates. Future work will reveal whether *Drosophila* hemocytes are 'antigen-presenting' cells, whether they act via cytokines, or in fact whether both mechanisms operate.

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Cell Adhesion: Separation of p120's Powers?

The catenin p120 is involved in many processes, including cell–cell adhesion and cancer. Recent work explores whether p120 independently regulates two key binding partners, RhoGTPase and cadherin.

Donald T. Fox[1] and Mark Peifer[1,2]

Regulation of cell–cell adhesion is critical for both morphogenesis and metastasis. Cell-adhesion complexes maintain and remodel tissues via linkage to the cytoskeleton. Regulated changes in adhesion are coordinated with cytoskeletal changes, thus directing cellular and tissue morphogenesis. Conversely, loss of cell–cell adhesion can promote tumor metastasis via changes in cell motility. Thus, examining regulators of adhesion and the cytoskeleton will advance our understanding of development and disease.

Despite its humble name, the p120 protein is extremely versatile, playing roles in adhesion, nuclear signaling, and cancer. p120 also binds to a formidable array of partners, including cadherins, which mediate cell–cell adhesion, and the cytoskeletal regulator Rho, a small GTPase. Understanding p120's multiple functions requires assigning particular functions to particular partners. While many p120 partners were initially identified *in vitro*, their *in vivo* relevance is now being addressed [1].

Several recent papers [2–5] argue that p120 regulates both cadherins and Rho in many cellular processes, but suggest that the question of whether p120 regulates these targets separately does not have a simple answer. p120 plays an important role at the interface of adhesion and cytoskeletal regulation during development and oncogenesis. Originally identified as a substrate of the Src oncogene, p120 was subsequently found to bind cadherins [1]. Loss-of-function studies confirmed that p120 promotes adhesion, at least in part, by inhibiting endocytosis of cadherins [6–9]. Recent *in vivo* work in mammals emphasized p120's importance in cadherin stabilization [2–5,10].

Overexpression studies identified another p120 target — RhoGTPase. p120 overexpression reduces cell contractility and actin-rich stress fibers, while increasing cell motility, at least in part, by inhibiting Rho and activating Rac and Cdc42 [11–13]. Rho can bind both p120 and α-catenin [14], suggesting that regulation might occur at cell junctions. However, E-cadherin