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VISIONS AND PERSPECTIVES

Developed to cull: how a master control gene of development turned into a regulator of innate immune homeostasis

V Zappavigna

Department of Animal Biology, University of Modena and Reggio Emilia, Modena, Italy

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Abstract

A striking novel role for the *Caudal* "master control" gene of development in the regulation of innate immune functions in insects has emerged. A recent study now adds further insight into the function of this homeobox gene in the maintenance of the immune homeostasis that is required to preserve the normal commensal community within the *Drosophila* gut. These results point to a possible more widespread co-option of developmental regulatory genes during evolution to add tissue- and/or organ-specific regulatory plasticity to innate immune systems.

Key words: innate immunity; homeostasis; insects; *Drosophila melanogaster*; homeobox genes; *Caudal*

In metazoa innate immunity represents the first barrier of defense against infections caused by various types of microorganisms. Insects, for instance, rely primarily on innate immunity to fight infectious microbes. An important branch of the immune defence system in these organisms is based on the production and secretion of antimicrobial peptides (AMPs). The inducible production of AMPs is one of the best-studied mechanisms of immune defence in insects. In *Drosophila melanogaster* the synthesis of AMPs can be triggered by the activation of three main signalling pathways: the Toll, Immune deficiency (Imd), and JNK pathways. Both the Toll and Imd pathways control the transcription of AMP genes via the activation of two *Drosophila* homologs of the NFkB transcription factor, Dorsal and Relish. AMPs, however, are synthesized not only in response to infection, but are also produced constitutively in healthy individuals in a tissue-, sex-, and gene-specific manner (reviewed in Uvell and Engstrom, 2007). Understanding the molecular mechanisms underlying the constitutive and inducible expressions of AMPs in various tissues represents thus an intriguing novel field of study. One of the innovative concepts that have already begun to emerge in this field is that the regulation of AMP expression may rely on the same gene regulatory networks that control cell fate during developmental processes. A beautiful example of this was published in a recent issue of Science by Ryu *et al.*(2008). In their work Ryu and co-wokers analyzed at the molecular level the immune interactions between commensal microbiota and the *Drosophila* gut. They found that, despite the chronical Imd-mediated high-level activation of Relish by gut commensal microorganisms, only a subset of its target genes was expressed, remarkably excluding AMPs. The reason for this selective exclusion of AMP gene expression was found in the specific repressive action of the Caudal (Cad) homeodomain transcription factor, as Ryu *et al.* (2008) elegantly demonstrate. *Caudal* had been previously shown to act as a master control gene in several crucial developmental processes in *Drosophila*, including the definition of the anteroposterior axis and gut development (Mlodzik and Gehring, 1987; Moreno and Morata, 1999; Lengval and Iwaki, 2002). In addition, Cad has been recently found to be crucial for constitutive AMP expression in salivary glands and ejaculatory duct epithelia, implicating for the first time this developmental regulatory gene in a constitutive innate immune strategy (Ryu et al., 2004). Ryu *et al.* (2008) now show that the knock-down of Cad expression in gut cells via transgenic RNAi restores the production of AMPs in the gut, indicating that Cad acts as a gut-specific transcriptional repressor of commensal-induced NFkB-dependent AMP expression. Strikingly, Cad knockdown in intestinal cells was also accompanied by a significant rise in gut epithelial cell apoptosis. As it turned out, gut cell death was induced as a secondary effect to AMP hyperactivation due to

Corresponding author:
Vincenzo Zappavigna
Department of Animal Biology
University of Modena and Reggio Emilia
Via Campi 213/D, 41100 Modena, Italy
E-mail: vincenzo.zappavigna@unimore.it

drastic changes in the gut commensal community structure. In particular two bacterial strains were shown to vary considerably in their abundance upon Cad knock-down. *A911* bacteria, which represents the dominant strain in the gut microbial community, were significantly reduced in number in Cad knockdown flies, whereas the *G707* strain, which is a normally a minor member of the commensal community in the *Drosophila* gut, emerged as a dominant commensal. *G707* bacteria revealed to be responsible for the observed induction of apoptosis in gut cells and the consequent rise in mortality of host flies. Interestingly, *G707* bacteria fed to animals with a normal gut commensal community did not induce apoptosis, and germ-free animals first colonised with *A911* bacteria prevented the growth of *G707* bacteria, indicating that the normal gut microbial community is sufficient to suppress the growth of pathogenic bacteria. *A911* bacteria were furthermore found to be sensitive to AMPs, whereas *G707* bacteria were much less so, thus explaining their rise in number in Cad knock-down AMP-expressing *Drosophila* guts.

Overall, the results by Ryu *et al.* (2008) show that the maintenance of the immune homeostasis required for the preservation of the normal commensal community of the *Drosophila* gut ultimately rests on the gut-specific repressive action of the Cad homeodomain transcription factor on AMP genes. *Drosophila* intestinal epithelia have thus evolved a remarkable immune strategy, which entails the recruitment of a developmental regulatory gene whose repressive action allows the selective survival of non-pathogenic commensal bacteria capable of maintaining homeostasis via colonization resistance. On a broader perspective, it is tempting to speculate that the co-option of developmental regulatory genes expressed in a tissue- and/or organ-specific manner may offer the unique evolutionary advantage of adding regulatory plasticity to the innate immune system. Indeed, the transcriptional control of AMPs by tissue-specific transcription factors would meet the needs for an infection-independent costitutive expression (or repression, as in the case of the *Drosophila* gut) that is tailored to obtain a spatially-differentiated immune defense. It is therefore not unlikely that *Cad* will represent the first example of a whole series of developmental "master control" genes that will reveal in the near future to play fundamental roles in the tissue- and/or organ-specific regulation of the innate immune system function.

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