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IMMUNOMETABOLISM

Mef2 in sickness and in health

> Mef2 … controls a switch from metabolic gene expression to immune-response gene expression during infection in flies

Infection can cause weight loss, but the link between infection-induced immune activation and loss of anabolic function is poorly understood. Now, researchers studying infection in *Drosophila melanogaster* have found that the transcription factor Mef2 (myocyte-specific enhancer factor 2) controls a switch from metabolic gene expression to immune-response gene expression during infection in flies.

Clark *et al.* used gene expression microarrays and *D. melanogaster* with targeted protein deficiencies (using RNA interference (RNAi)) to identify the pathways and the transcriptional networks that regulate the response to infection. By clustering the genes that were co-regulated and that shared transcription factor-binding sites, the authors identified *Mef2* as a potential regulator of both immune response genes and metabolic activities. In the functional RNAi screens, *Mef2* was one of five genes that were required for *D. melanogaster* survival following *Mycobacterium marinum* infection. Moreover, flies with a targeted knockdown of *Mef2* expression in the fat body (which is equivalent to the mammalian liver and adipose tissue) showed increased susceptibility to infection with several other micro-organisms (*Listeria monocytogenes*, *Enterobacter cloacae* and *Candida albicans*), which target the Toll or Imd pathways.

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Further analysis of the microarray data revealed that a cluster of genes predicted to be targeted by Mef2 contained metabolic enzymes that were rapidly and transiently downregulated 3–6 hours after infection. Similarly, the expression of a group of enzymes that are involved in glycogenesis and lipogenesis was lower in *Mef2*-knockdown *D. melanogaster* than in control flies, and *Mef2*-knockdown flies died more rapidly when starved. This suggests that a metabolic defect in *Mef2*-knockdown flies contributes to their poor survival after infection by decreasing their ability to withstand infection-induced weight loss.

In addition to this metabolic defect, *Mef2*-knockdown *D. melanogaster* showed a marked reduction in their expression of various antimicrobial peptides (AMPs) in response to infection. Analysis of putative regulatory regions from AMP genes consistently revealed the presence of a predicted Mef2-binding site that overlapped with a TATA box (which is bound by TATA-binding protein (Tbp)). This Mef2–TATA box-binding site was shown to be required for the induction of AMP expression *in vivo* using flies expressing wild-type or mutant reporter constructs. Further experiments indicated that Mef2 and Tbp form a complex on the Mef2–TATA box-binding sites of numerous AMPs, as well as of other immune genes, and that this is required for the normal transcriptional induction of these genes.

Microarray data also showed that when the expression of antimicrobial genes was induced, the expression of metabolic genes was reduced. How is this counter-regulation achieved? Mef2 was found to be phosphorylated on a conserved region of its DNA-binding domain in healthy *D. melanogaster* but this phosphorylation was lost following infection. Experiments using flies expressing wild-type non-phosphorylatable Mef2 or a constitutively phosphorylated form of Mef2 showed that only unphosphorylated forms of Mef2 associate with Tbp. So, the loss of Mef2 phosphorylation that occurs following infection facilitates the formation of the Mef2–Tbp complexes that are responsible for the induction of AMP expression. Consistent with the idea that phosphorylation switches Mef2 target gene repertoires, only the phosphorylatable forms of Mef2 promoted expression of metabolic genes.

So, in flies, phosphorylation of Mef2 controls a switch between ensuring storage of fat and glycogen and mounting a protective response to infection.

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ORIGINAL RESEARCH PAPER Clark, R. I. *et al.* MEF2 is an *in vivo* immune-metabolic switch. *Cell* **155**, 435–447 (2013)