

As intermediates between signaling pathways and the genetic code, transcription factors govern biological processes via direct regulation of gene expression. The Activating transcription factor 3 (ATF3) is a member of the ATF/CREB family of sequence-specific, DNA-binding basic leucine zipper (bZIP) transcription factors that has emerged as an important hub of adaptive response. Regulated at the level of transcription, investigations in mammals have determined that ATF3 expression is induced in response to diverse signaling inputs. Chronic misregulation of ATF3 is detrimental to organismal health and has been implicated in tumorigenesis. However, the contribution of ATF3 to cellular responses remains unclear, as the genetic programs under direct control of ATF3 remain incompletely described.

Using the *Drosophila melanogaster* model organism, we establish that *Atf3*, the single ortholog of mammalian ATF3, safeguards metabolic and immune system homeostasis. Loss of *atf3* results in chronic inflammation and starvation responses mounted primarily by the larval gut epithelium, while the fat body suffers lipid overload, causing energy imbalance and death throughout larval stages. ChIP-seq analysis determined that targets of *Atf3* gene, which encode proteins central to cytoskeleton dynamics and adhesion, minimally overlap with genes differentially expressed in *atf3* mutants. This suggests that the transcriptional signature of *atf3* mutants reflects secondary consequences of *Atf3* deficiency. Subsequent *in vivo* validation of ChIP-seq results determined that *Atf3* is a potent regulator of epithelial biology via positive and negative regulation of target gene expression. Epithelial clones overexpressing *Atf3* are enriched for basolateral proteins at the expense of apical identity. Strikingly, *Atf3* functions downstream of the membrane associated Scribble polarity module. Depleting either scribble or discs large 1 induces *atf3* expression. Furthermore, *Atf3* genetically interacts with the Scribble complex. Loss of *atf3* suppresses differentiation and polarity defects in cells deficient for either scribble or discs large 1. Thus, *Atf3* presents a novel link between epithelial cell polarity and regulation of specific gene expression programs.