PERSPECTIVES: IMMUNOLOGY

Regulating the Regulator

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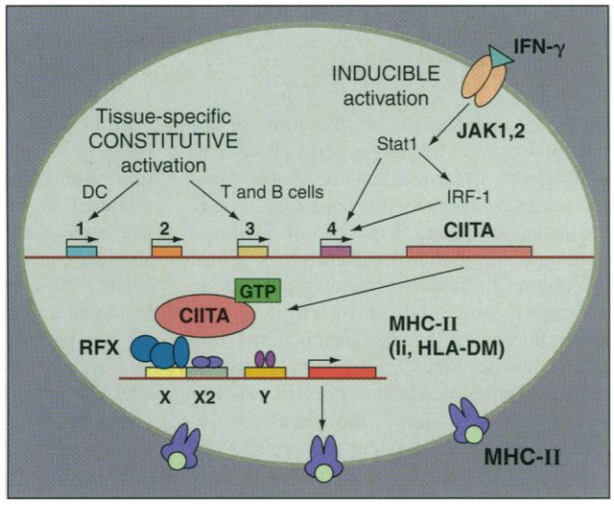
The immune system's remarkable molecular specificity, which allows the subtle discrimination between self and non-self, is well-established. Less clear is how activation of lymphocytes, the immune cells of the body that dispatch foreign invaders, is regulated. Tightly controlled expression of the major histocompatibility complex (MHC) class II gene family is one way in which T lymphocyte activity can be modulated. These genes encode a series of immunoglobulin-like proteins (expressed on the surface of antigen-presenting cells such as dendritic cells or activated macrophages) that help T cells to recognize foreign antigen. Many essential features of the immune system—from the generation of self-tolerance to the induction of an immune response—depend on MHC class II molecules. Thus, it is curious that the expression of the entire class II gene family is under the direct control of one master regulator, the transcription factor CIITA (*1*). Ultimately, CIITA determines the highly selective spatial and temporal pattern of MHC class II gene expression, which in turn modulates the immune response (*2*). A new twist to the story is reported by Harton *et al.* on page 1402 of this issue (*3*). They show that CIITA is able to bind guanosine triphosphate (GTP), a signaling molecule involved in many cellular responses. When bound to GTP, CIITA migrates to the nucleus, the site of action of transcription factors. Mutations in CIITA that abrogate its GTP-binding activity decrease nuclear translocation of CIITA and transcription of target genes.

The very tight regulation of MHC class II genes restricts their expression to a few specialized cells of the immune system. The biological consequences of a breakdown in this tight control are seen in disorders such as alloreactivity, autoimmunity, inflammation, or the response to superantigens. Much of what we know about the complexities of MHC class II expression derives from the study of a rare primary immunodeficiency disease in which cells do not express MHC class II proteins (*2*). Class II genes themselves are normal but their expression is abolished by mutations in transcription factor genes encoding either CIITA (*1*) or one of the three components of a DNA-binding complex—RFX5 (*4*), RFXAP (*5*), or RFX-ANK (*6*). CIITA itself does not bind directly to the DNA but is likely to interact with the RFX complex (see the figure).



Serving the master. CIITA (red) is a master transcription factor that is essential for expression of MHC class II genes (and also Ii and HLA-DM genes). When bound to GTP (green), it migrates to the nucleus and interacts with a DNA-binding complex RFX (blue), which is bound to the class II gene promoters. Expression of CIITA is controlled by four separate promoters: Promoters 1 and 3 are specific for its expression in dendritic cells (DC), and in T and B lymphocytes, respectively. Promoter 4 is responsible for inducing CIITA expression in response to interferon-γ (IFN-γ).

Although they are expressed ubiquitously in all tissues, the components of the RFX DNA-binding complex are all essential and highly specific for activating class II gene expression (*2*). CIITA is not only essential and specific but also sufficient for MHC class II gene expression (*1*). Numerous studies in MHC class II positive and negative tissues, in situations where gene expression is permanently switched on (constitutive) or induced (for example, in response to growth factors) have established that CIITA is the master regulator of MHC class II genes (*1, 2*). It is clear that control of CIITA is essential for regulation of MHC class II expression and T lymphocyte activation. Intriguingly, the expression of CIITA itself is controlled by several separate promoters (*7*). Promoters 1 and 3 are specific for CIITA expression in dendritic cells and lymphocytes, respectively, whereas promoter 4 is responsible for the induction of CIITA by interferon-γ (*7*).

CIITA is not itself a DNA-binding protein. It seems to act as a coactivator, binding to RFX and other DNA-binding complexes that themselves are bound to the promoters of MHC class II genes (*3*)—although such interactions have not yet been documented under truly physiological conditions. Another level of CIITA regulation is suggested by the finding of three GTP-binding motifs in this master transcription factor. Deletion mutations in these motifs result in loss of CIITA transcriptional activity (*3, 8*). Harton *et al.* propose that CIITA is unique among the many proteins that bear GTP-binding motifs (*9*) in several respects: Alteration of the GTP-binding sites (by deletion) inactivates CIITA; this transcription factor does not have GTPase activity, that is, it cannot break down GTP; only GTP-bound CIITA, but not the mutated unbound form, is able to migrate to the nucleus. Although there is no physiological evidence as yet, it is tempting to speculate that CIITA is regulated by the levels of guanosine nucleotides in the cell. However, one argument against posttranslational control of CIITA through modulating nuclear translocation is provided by the excellent quantitative correlation between CIITA expression (under a variety of physiological conditions and in multiple cell types) and the level of MHC class II mRNA that it elicits (*10*). Direct biological evidence for posttranslational control of CIITA activity will be the next step in further unraveling the mystery of how the regulator is regulated.

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