nature immunology

Modifying immunity

Post-transcriptional and post-translational modifications exert subtle yet profound influences on all aspects of immunity.

Many regulatory networks govern gene-expression patterns; however, additional regulatory steps act after genes have been expressed. These include factors that influence the turnover and translation of mRNA, as well as post-translational modifications that regulate the stability and function of protein. In this issue of *Nature Immunology*, we provide a series of specially commissioned Review articles that survey the complex web of post-transcriptional and post-translational modifications that underpin the activity and development of the immune system (http://www.nature.com/ni/focus/ptm).

Recent years have witnessed an explosion of interest in the role of noncoding RNAs and their seemingly ubiquitous ability to control gene expression. These operate in a more subtle manner than do transcription factors by arresting the translation of mRNA but are no less critical for the smooth running of the immune system. Noncoding RNAs include short microRNAs 21–23 nucleotides in length and their lesser known 'cousins', long noncoding RNAs, which are more than 200 nucleotides in length. The mode of action and widespread importance of microRNAs have been well described, but the role of long noncoding RNAs is only now beginning to be appreciated. Martin Turner and colleagues survey the latest findings on how long noncoding RNAs control gene expression and their importance to the immune system. Another mechanism of gene regulation common in the immune system operates via the 3′ untranslated regions of mRNAs, which can contain multiple regulatory sequences. Nowhere is this better exemplified than in interleukin-encoding mRNAs, many of which have large 3′ untranslated regions often vastly greater than their coding sequence, which hints at still-hidden depths of regulation of this group of cytokines.

In a related Review, Dimitris Kontoyiannis and colleagues consider another level of mRNA regulation: that offered by RNA-binding proteins (RBPs). These are a heterogeneous collection of factors that have not only RNA-binding domains but also modular domains that enable protein-protein interactions or direct modifications of RNA. RBPs typically operate by degrading mRNAs, with several interrelated pathways being involved in this process. For example, deadenylation of the 3′ poly(A) tail and 5′ decapping are the predominant degradative processes overseen by RBPs in cells of the immune system. Abundant evidence has linked RBPs to almost every facet of the immune response, ranging from thymopoiesis and immunological homeostasis to inflammation and antiviral responses.

Ciriaco Piccirillo and colleagues review how selective translation is emerging as a key process for controlling protein abundance in both innate and adaptive immunity. One prominent example of this is the kinase PKR, which is activated by type 1 interferons and shuts down the translation of mRNA in response to viral infection. Attention has also focused on the metabolic checkpoint kinase mTOR, which can skew translation toward less-abundant cytokine-encoding transcripts. Simply switching the activity of mTOR on or off can push the immune system from quiescence to full-blown inflammation. Drugs in widespread clinical use, such as the mTOR inhibitor rapamycin, tap directly into this process by selectively altering the translation of key immunological factors.

Phosphorylation and ubiquitination are the best characterized types of post-translational modification, but a whole slew of other modifications also exist whose importance for the immune system is only now being appreciated. Kerri Mowen and Michael David review the role of such 'unconventional' modifications in signaling by cells of the immune system. For example, the proinflammatory transcription factor NF-κB undergoes both methylation and acetylation of lysine in addition to its better known phosphorylation of serine. Such modifications can, among other effects, alter the ability of NF-κB to bind DNA and thereby 'fine tune' its transcriptional activity. Methylation is not directed solely at lysine, as methylation of arginine in various proteins is emerging as an important event downstream of antigen receptors on both B cells and T cells. Post-translational modifications such as nitrosylation, which is often a consequence of the production of nitric oxide by macrophages, can trigger apoptosis or inactivate important targets such as the NLRP3 inflammasome. In addition to altering the function or abundance of cellular proteins, certain modifications can be detrimental. Citrullination, for example, can trigger autoimmunity by breaking tolerance through the generation of neoantigens. Indeed, citrullinated proteins have become a key diagnostic marker of rheumatoid arthritis.

Philip Cohen reviews how mutations in genes encoding E3 ligases, ubiquitin-binding proteins and kinases can lead to human disease. Approximately 10% of all proteins in humans are involved in either phosphorylation or ubiquitination, so it is perhaps inevitable that many diseases should arise from defects in these systems. Because appropriate regulation of phosphorylation and ubiquitination is 'system critical' for cells of the immune system, loss-of-function mutations in genes encoding molecules involved in these processes often results in severe immunodeficiency or spontaneous autoinflammatory disease. For example, mutation of the gene encoding the kinase IRAK4 manifests as enhanced susceptibility to pyogenic infection, whereas mutation of the gene encoding the kinase ALPK1 results in predisposition to inflammatory bowel disease. Study of mutations in these immunologically relevant genes can also throw light onto the fundamental workings of the human immune system and occasionally offer sobering insights into discrepancies with animal models.

It is clear that the function of mRNAs and proteins is controlled by far more than simple abundance alone. The coming years will undoubtedly witness the discovery of additional forms of post-transcriptional modifications with unforeseen effects on the function of the immune system. Deeper understanding of how these modifications control the stability and translatability of mRNA or protein activity could offer opportunities for the therapeutic targeting of a wide range of immunological conditions.