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Introduction: Dynamics of RNA Regulation in the Immune System Special Issue

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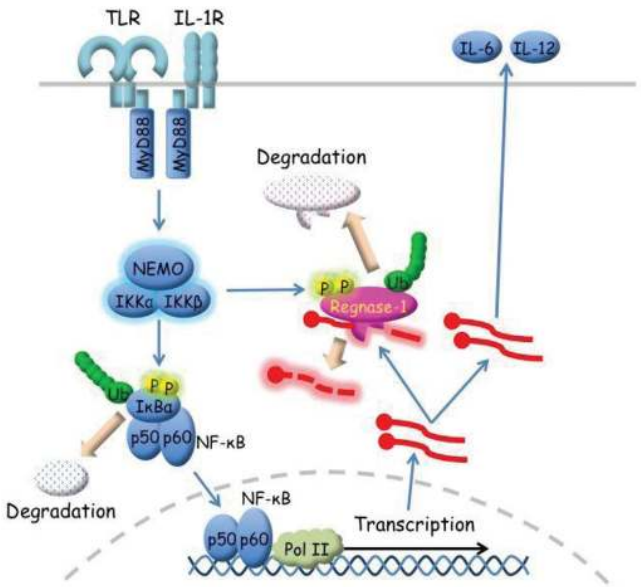
Guest Editors

The publication of the human genome was the culmination of decades of advance in research and cooperation and has, as hoped, provided not only a foundation but also a springboard for further study. One of the consequences has been an increasing appreciation of the many roles of the various forms of RNA in the function of all cell types at different times. Diverse roles for RNA in control of catalysis, gene expression, signaling and communication have been established and are continuingly being defined and expanded. As expected, this is true within the immune system, where tried and tested protective mechanisms that have proved effective in evolution must be continuously supplemented by flexible and innovative responses to new challenges.

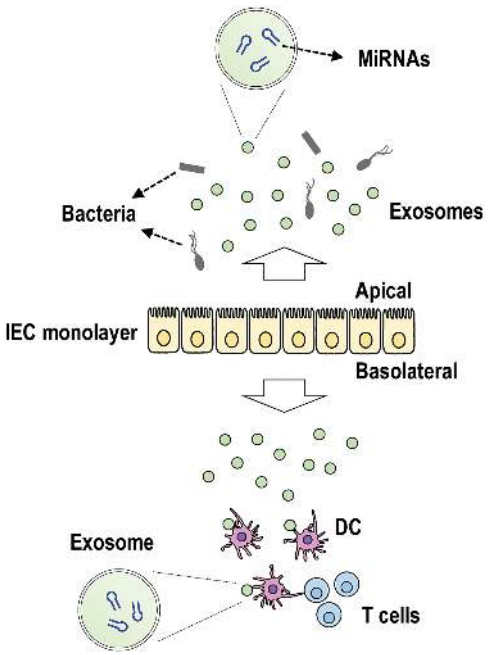
This Special Issue contains five review articles that update us on many of the new discoveries and highlight areas where progress will continue. We would like to thank all of the authors for these excellent and thought-provoking articles.

In our first article, Kazuhiko Maeda and Shizuo Akira discuss in detail three CCCH-type zinc-finger proteins (ZFPs), which bind RNA and control post-transcriptional regulation of cytokine mRNAs (1).



As dissected here, these ZFPs are induced by different factors (e.g. cytokines and TLR or TCR ligation) and have some shared and some distinct properties and targets (e.g. various cytokines, chemokines and ICOS); TNF-α and IL-6 are especially well-characterized examples. Tristetraprolin (TTP) binds adenine- and uridine-rich elements (AREs) in its target mRNAs and destabilizes them to dampen excessive inflammation. TTP deficiency causes cachexia, arthritis and autoimmunity. Roquin-1 is a functional E3 ubiquitin ligase that binds a constitutive decay element (CDE) downstream of the ARE in the 3′-UTR of target mRNAs; in particular, it modulates the development of T_{fh} and T_h17 cells. The endonuclease Regnase-1 binds a stem–loop structure at the 3′-UTR of target mRNA, again degrading it (see figure to the left). Regnase-1 deficiency results in severe inflammatory autoimmunity. Finally, the authors discuss interactions of these ZFPs with microRNAs (miRNAs).

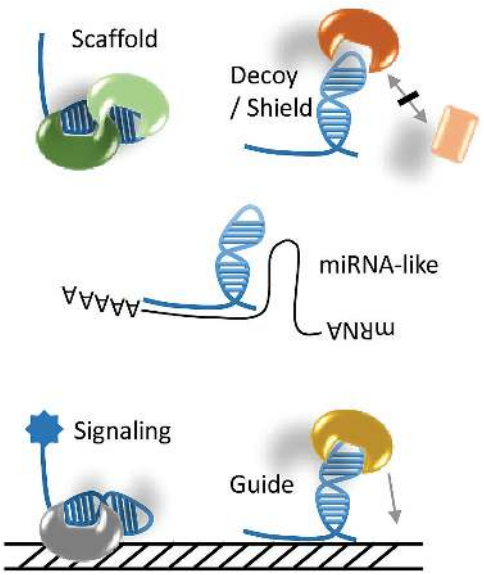
miRNAs are small (average 22 nucleotides) non-coding RNAs that bind the 3′-UTR of mRNAs and are known to fine-tune diverse biological processes including the function and regulation of immune responses. In their article, Eun Jeong Park, Motomu Shimaoka and Hiroshi Kiyono concentrate on the control of mucosal immune responses by miRNAs (2).



Deficiency of biogenesis of miRNAs mediated by the ribonuclease Dicer selectively in the intestine causes a wide range of abnormalities to the mucosal immune system. The authors describe the role of specific miRNAs in a wide range of

intestinal cell types: intestinal epithelial cells, M cells, lymphocytes, plasma cells, dendritic cells and macrophages. They then detail the involvement of specific miRNAs implicated in inflammatory bowel disease (IBD) and collate findings of increased miRNAs in serum and colon tissue in Crohn's disease or ulcerative colitis and their potential as biomarkers in IBD and other diseases such as colorectal cancers. Finally, the authors discuss using exosomes as vehicles for transporting miRNAs and the potential for therapeutic applications.

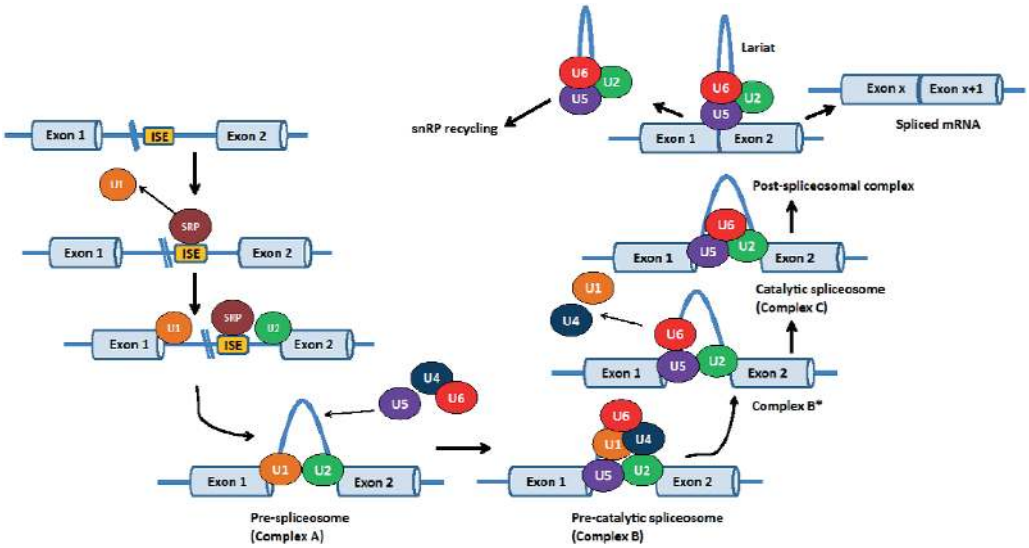
Long non-protein-coding RNAs (lncRNAs) are over 200 nucleotides in length. Most cell types express lncRNAs but they mostly operate in the nucleus and show greater tissue- and stage-specificity than coding mRNAs do. In our third article, Wooseok Seo and Ichiro Taniuchi (3) begin by describing specific lncRNAs that are expressed in hematopoietic stem cells.



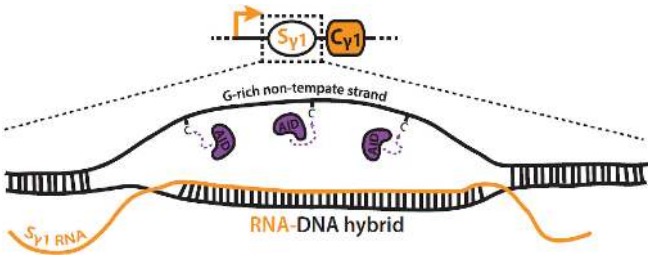
More lncRNAs appear to be expressed during erythropoiesis and their interactions are being investigated (see figure to the left; lncRNAs are shown in blue). Several lncRNAs have been demonstrated during myelopoiesis and differentiation of specific myeloid cell types. The authors then detail the roles of lncRNAs in genes and pathways crucial for innate immune responses in dendritic cells, macrophages, monocytes, granulocytes and fibroblasts. Similarly, specific lncRNAs have been identified in adaptive immune responses (T_h1, T_h2 and T_h17 cells). As discussed, identification of lncRNAs in the immune system is expanding rapidly but the molecular interactions are largely unexplored and offer numerous opportunities for future research, for example challenging the classical categories of coding RNAs versus non-coding RNAs.

Most gene sequences can be differentially expressed, which greatly increases the repertoire of available products. In their article, Annalisa Schaub and Elke Glasmacher discuss alternative splicing (AS) of RNA molecules in immune cells (4). They start by detailing the molecular mechanisms in the spliceosome (see figure below). They also outline how splicing might occur alongside transcription in macrophages and T cells. They describe the nuclear compartments (e.g. nuclear speckles, paraspeckles, Cajal bodies and the novel compartment InSac) in which AS occurs for specific mRNAs in, for example, lymphocytes and medullary thymic epithelial cells. The authors then summarize genome-wide association studies that have identified AS events in macrophages, dendritic cells, T cells and B cells. They describe specific examples associated with lineage differentiation, cell signaling, maturation, activation and function, affecting, for example, TLRs, MyD88 and immunoglobulins. Mutations in splicing factors have been reported for several cancer types and autoimmune diseases but the authors conclude that this field is still in its infancy, with potential for new discoveries.

Discoveries about the characteristics and mechanisms of immunoglobulin class switch recombination (CSR) have provoked numerous studies over many decades. The insights gained have provided discoveries that proved ground-breaking in several fields as different aspects of the process has been revealed.



In the final article, William T. Yewdell and Jayanta Chaudhuri guide us through this story from a historical perspective (5).



The crucial role of the DNA-modifying enzyme AID (activation-induced cytidine deaminase) in CSR was reported at the turn of the century but a role for non-coding RNAs [germline transcripts (GLTs)] had been discovered in the 1980s. The authors continue to describe the characterization of CSR while interweaving the structural and molecular characterization of how processed GLTs (in G-quadruplex structures) allow AID to access and target ssDNA in the immunoglobulin heavy-chain locus (see figure). Direct AID–RNA binding appears crucial for this, and perhaps for AID's enzyme activity, and the authors illustrate how this can occur in *trans* or *cis*.

Like our other articles, this shows that, over the years, we have learned so much about how DNA and RNA function within us; but there is much decoding still to do.

References

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