EDITORIAL

RNA modifications—a regulatory dimension yet to be deciphered in immunity

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Analogous to the epigenome as the sum of modifications to histones and DNA, the epitranscriptome is the sum of all RNA modifications. The epitranscriptome comprises >170 different RNA modifications, however, we only begin to understand the function of a few. Particularly their roles in mammalian cell development and function remain obscure. RNA modifications change the chemical properties of RNA allowing for interactions with RNA-binding proteins but also changing the RNA life-cycle including splicing, stability, location, and translation efficiency. Consequently, they shape the transcriptome and proteome.

Two internal RNA modifications stand out as particularly abundant and relevant for the dynamic regulation of cell-intrinsic processes, namely RNA methylation (RNA^{meth}) and isomerization of uridine to pseudouridine (Ψ).

Studies in lower organisms such as yeast helped to understand the physico-chemical properties conferred by RNA^{meth} and Ψ as well as mechanisms of action of the respective installing enzymes. They also provided insight into the importance of conditional regulation of RNA modifications in contexts that require fast cellular adaptation such as for Ψ during nutrient deprivation or heat-shock in yeast [1–4]. Similarly, in mammalian cells the Ψ mRNA landscape undergoes dynamic changes in response to serum starvation, hydrogen peroxide or heat-shock [1, 5]. Overall, while RNA modifications and their installing enzyme complexes are largely conserved from lower organisms to human, the study thereof in mammalian cells and mammalian model systems has long been hampered by the lack of sufficiently sensitive research tools and tools that allow the functional dissection of the network of contributing writers, erasers, and readers of RNA modifications.

Owed to recent technological and methodological advances of the recent past, such as Crispr/Cas and advances in next-generation sequencing (NGS), epitranscriptomic studies have now taken the leap from lower organisms to functional-mechanistic studies in in vitro and in vivo mammalian model systems. In parallel, human disease conditions have been linked to a dysfunctional epitranscriptome. Moreover, recent findings in (haematopoietic) stem cell research, haematological malignancies, and immunity illustrate the importance of understanding how the epitranscriptome governs immune cell differentiation processes as a novel master regulatory level.

The core catalytic enzyme for adenosine methylation in RNA (m^6A) is Mettl3. In addition, 'readers' (modification-binding proteins) and 'erasers' (modification-removing proteins) have been suggested, however, the concept and necessity of erasers is contested given that the short half-life of RNA may make modification erasers redundant and their specificity for RNA^{meth} residues may be low [5]. Driven by the methodological simplicity of 'one gene knockout (Mettl3) = complete RNA^{meth} deficiency' and the advent of high-sensitivity detection methods, this subfield is currently dominating mammalian epitranscriptomics research with very promising insights into RNA modification-mediated regulation of cell development and function.

With focus on immune cells, RNA^{meth} governs haematopoiesis and leukemogenesis [6]. In haematopoietic stem cells, it regulates self-renewal, and its dysregulation in progenitor cells plays a vital role in haematopoietic malignancies such as acute myeloid and acute lymphocytic leukaemia. Components of the RNA^{meth} network are hence becoming a focus of translational studies. Inhibitors of the central RNA^{meth} enzyme Mettl3 as well as inhibitors for the RNA^{meth} eraser FTO are under development for application in (non-) haematological cancers [6]. In further immune cell development and function, RNA^{meth} has been shown to regulate immune responses by promoting T cell and dendritic cell activation, as well as myeloid cell activation and NK cell activity [7–10]. Mettl3 inhibitors may hence also be of interest in an autoimmune context. Along these lines, the m^6A reader IMP2 has been identified as potential target for therapeutic intervention in the IL-17/TNFα signalling axis in cytokine-driven autoimmune inflammation [11]. However, Mettl3 has also been shown to regulate immune tolerance by sustaining regulatory T cell (Treg) functions [12], implying that Mettl3 inhibitors in autoimmune contexts may reduce T cell activation but simultaneously negatively affect peripheral tolerance exerted by Treg. Hence, our understanding of the (partially opposing) roles of RNA methylation in different immune subsets is still very limited and will hamper clinical translation of inhibitors until delineated.

The pseudouridylation network differs from the RNA^{meth} network in that 13 non-redundant pseudouridine synthases catalyse the isomerization of uridine to Ψ. No erasers have been identified to date, implying that the turnover of Ψ may be passive and solely regulated by dynamic and conditional expression of the synthases. The conversion of uridine into Ψ changes physico-chemical and thermostability properties of the nucleoside. The view that Ψ function is exclusively governed by its structural characteristics however, has recently been challenged by the identification of a first Ψ reader in yeast and it has been suggested that differential 'reading' of Ψ post-transcriptionally regulates coordination between global translation (tRNA) and gene-specific translation (mRNA) [13].

Despite decades of structural and functional studies of Ψ in yeast, mammalian Ψ research is substantially lagging compared to insights gained recently on RNA^{meth} in immune cells among others owed to the complexity of 13 installing synthases. However, the advent of high-throughput Ψ-sequencing discovered a complex Ψ landscape that is highly inducible [2, 14, 15]. The cell type-specific expression pattern of 13 Ψ synthases likely allow for adaptable pseudouridylation and hence may contribute to different mRNA Ψ landscapes in different immune subsets and different developmental or functional cell states. This implies that Ψ may be able (or necessary) to rapidly and dynamically rewire the transcriptome/proteome [1] and thereby to impact cell fate and functional decisions analogous to RNA^{meth}.

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Given the non-redundant function of the various Ψ synthases and despite partial deficiency of Ψ in single synthase malfunctions, defects in the pseudouridylation network have demonstrated a vital role for Ψ in various mammalian cell types, including haematopoietic cells and mutations in different synthases have been correlated with disease in humans.

Together, the study of RNA modifications in immune cells and human diseases has only recently began and we need to acquire a comprehensive understanding on how RNA modifications regulate the development and differentiation of immune cell lineages and shape immune responses to understand causal relationships between defects and disease.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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