Epitranscriptomic Modulation of Type I IFN Pathway to Treat Cancer and Autoimmune, Inflammatory, and Infectious Diseases

An innovative and targeted approache to treat cancer and autoimmune, inflammatory, and infectious diseases

Technology

The Mohr Lab has identified the RNA N^6-adenosine (m^6A) methyltransferase subunits METTL3 and METTL14, and the m^6A demethylase ALKBH5 as critical components of epitranscriptomic regulation of genes involved in the Type I interferon (IFN) pathway. As described in published work (*Rubio et al. Genes Dev 2018*), the team has shown that presence of cytoplasmic double-strand DNA (dsDNA) or infection with human cytomegalovirus (HCMV), a double-stranded DNA virus, in cells triggers interferon production. Further, they have demonstrated that modulation of interferon beta 1 (IFNB1) mRNA, and thus IFNβ cytokine production, is controlled by m^6A modifications, as nascent IFNB1 mRNA accumulation was stimulated by METTL3/METTL14-depletion and restricted by ALKBH5-depletion. This work establishes that m^6A RNA modification enzymes regulate cellular responses to dsDNA-sensing, which shapes host immunity and contributes to pathogenesis of autoimmune diseases. The inhibition of activity or expression of these m^6A machinery enzymes modulates the cell-intrinsic innate immune response. Cells exposed to dsDNA following ALKBH5-depletion differentially-expressed genes regulating anti-viral immune responses, while METTL14-depletion altered pathways involving metabolic reprogramming, stress responses, and aging. In proof of concept work, the Mohr Lab has shown that Rhein, an mRNA N6-methyladenine demethylase inhibitor, reduces IFNB1 mRNA accumulation in response to primary human fibroblasts' interaction with dsDNA. This pharmacological validation establishes that inhibiting METTL3, METTL14, or ALKBH5 to modulate enzyme expression and/or function is a promising and tractable strategy for combating abnormal interferon production in autoimmune diseases as well as cancer, inflammatory and infectious diseases.

Background

Recent studies have shown that up to 10% of the global population is now affected by an autoimmune disease. Current treatment methods, such as immunosuppressive agents, are hindered by non-specificity, resulting in suboptimal efficacy and off-target effects. Dysregulation of Type I interferons is implicated in the pathophysiology of autoimmune and viral diseases, as IFN-I pathway cytokines are responsible for inflammation modulation and the anti-viral response. The IFN-I pathway is also involved in cancer cell proliferation and virus-induced tumorigenesis. Previous research has shown that N6-adenosine methylation (m^6A) modification plays a key role in modulating the IFN-I pathway. RNA methyltransferases METTL3 and METTL14 are two critical 'writer' proteins in the m^6A complex. Together, they recognize specific RNA sequences, leading to the cotranscriptional methylation of N6-adenosine, an important modification for RNA stability and translation. ALKBH5 is an RNA demethylase that removes the

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methyl group from m^6A-modified RNA molecules. This 'eraser' function allows for dynamic, reversible regulation of the m^6A modification, influencing RNA processing and the response to stress and DNA damage. Given the increasing prevalence of autoimmune diseases and lack of efficacious treatment options, there is a substantial unmet need for new therapeutic strategies to mitigate symptom burden stemming from IFN-I cytokine dysregulation. METTL3, METTL14, and ALKBH5 enzymes represent promising targets for regulating the IFN-I pathway.

Applications

- Treatment of autoimmune and inflammatory diseases: Including systemic lupus erythematosus, rheumatoid arthritis, chronic inflammation, multiple sclerosis, interferonopathies
- Treatment of infectious diseases: Including viral infections, fungal infections, and bacterial infection
- Treatment of cancer: Including renal cell carcinoma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, skin cancer

Advantages

- **Pharmacologically tractable targets:** Selective agents, including siRNAs, METTL3 inhibitors, and small molecule inhibitors (Rhein), have demonstrated potential for modulating expression and function of METTL3 and ALKBH5 enzymes
- **Well-characterized, disease-implicated signaling pathway:** The IFN-I pathway has previously been implicated in multiple conditions, including dermatomyositis, type 1 diabetes, Sjögren's syndrome, hepatitis B, hepatitis C, HIV, psoriasis, neurodegenerative diseases, and cancer
- **Mono- or combination therapies:** Enzyme inhibitors can be used independently and/or in combination with known chemotherapeutic, antiviral, antifungal, antibacterial, and immunosuppressant agents

Development Status

Work is ongoing.

Intellectual Property

A U.S. non-provisional patent application has been filed covering the methods of use for the Type I IFN pathway modulation (US 2021/0164992A1).

References

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