AUTOIMMUNE DISEASES

Suppressing autoimmunity with mRNA vaccines

The key to treating autoimmune diseases is to generate antigen tolerance without compromising the normal immune response. This is challenging as treatments that promote tolerance to specific disease-related proteins are difficult to develop and general immunosuppressants can render patients vulnerable to other infections. Now, a team led by Ugur Sahin has designed an mRNA vaccine that can restore tolerance to myelin proteins in mice, reducing the severity of multiple sclerosis-like symptoms, while maintaining the immune response towards other antigens.

Multiple sclerosis occurs when peripheral immune tolerance fails and T cells attack myelin, destroying the insulating sheath around nerve fibres. Previous attempts to restore such immune tolerance have been hampered by the heterogeneity of the disease, as the antigen spread is unique to the patient and so identifying a specific antigen for tolerance is difficult.

The authors wanted to mimic the natural mechanisms of immune tolerance, in which self-antigens are presented by dendritic cells in lymphoid tissues. To do this, they designed a vaccine consisting of a lipid nanoparticle packed with an mRNA that encodes one of the epitopes of myelin oligodendrocyte glycoprotein ($MOG_{35–55}$), which is one of the main proteins of the myelin sheath.

To avoid activation of Toll-like receptor signalling and subsequent release of IFNα — which is triggered by exogenous mRNAs and generates an immune response — they replaced uridine with 1-methylpseudouridine (m1Ψ) in the designed mRNA.

Next, the authors immunized C57BL/6 mice with the modified mRNA vaccine ($MOG_{35–55}$m1Ψ) and an analogous vaccine containing unmodified mRNA with the same sequence as a control, and assessed antigen presentation by dendritic cells and expansion of T cell populations. Both vaccines induced the expansion of $MOG_{35–55}$-specific T cells, but this expansion was higher in mice immunized with the $MOG_{35–55}$m1Ψ mRNA vaccine. Interestingly, only the $MOG_{35–55}$m1Ψ mRNA vaccine induced regulatory T cells (T_{reg} cells) — a subpopulation of T cells that suppress the immune response, maintain tolerance to self-antigens and prevent autoimmunity. Conversely, the unmodified mRNA vaccine induced expression of proinflammatory cytokines, whereas the modified vaccine did not. Importantly, the authors confirmed that immunization with $MOG_{35–55}$m1Ψ mRNA vaccine did not compromise T effector cell function towards other antigens, and that the induced tolerance was self-antigen-specific.

Next, they studied the potential for the vaccine to induce tolerance in mice with $MOG_{35–55}$-induced experimental autoimmune encephalomyelitis (EAE), a clinically relevant mouse model of multiple sclerosis. Treatment with the $MOG_{35–55}$m1Ψ mRNA vaccine prior to disease onset prevented all clinical signs of EAE in mice. In mice in which treatment was administered after disease onset and in which paralysis of the tail or the hindlimbs was noted, the vaccine prevented further progression and restored motor functions. Further analysis showed reduction of demyelination of the spinal cord, and of levels of infiltrating pro-inflammatory T cells, whereas levels of T_{reg} cells and expression of immune inhibitory receptors such as ICOS, LAG3, PD1, CTLA4 or TIGIT were markedly increased.

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The authors also developed a vaccine that included a mix of mRNAs encoding five different epitopes from myelin proteins that drive EAE in a complex mouse model ($MOG_{35–55}$, two epitopes from proteolipid protein ($PLP_{139–151}$, $PLP_{178–191}$), one epitope from myelin basic protein ($MBP_{84–104}$), and one from myelin-associated oligodendrocytic basic protein ($MOBP_{15–36}$)). The mixture of m1Ψ mRNAs coding for the five autoantigenic epitopes was effective in treating the disease, but, interestingly, the $MOG_{35–55}$m1Ψ mRNA vaccine was almost as effective as the cocktail. The authors suggest that this might be because activation of T_{reg} cells against a strong bystander epitope can repress T effector cells that target other antigens.

As we have seen with the recent vaccines for COVID-19, mRNA vaccines are a versatile platform that can be produced rapidly and in a cost-effective way. With their mRNA vaccine, Sahin and colleagues have shown that mRNA vaccines can also be used to turn down an unwanted immune response, and that selective delivery of autoantigens into dendritic cells in lymphoid tissues is an effective way to induce and maintain natural peripheral tolerance. Therefore, this approach could be explored for the treatment of other autoimmune diseases.

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