A potential therapeutic vaccine strategy for a subset of myeloproliferative neoplasms

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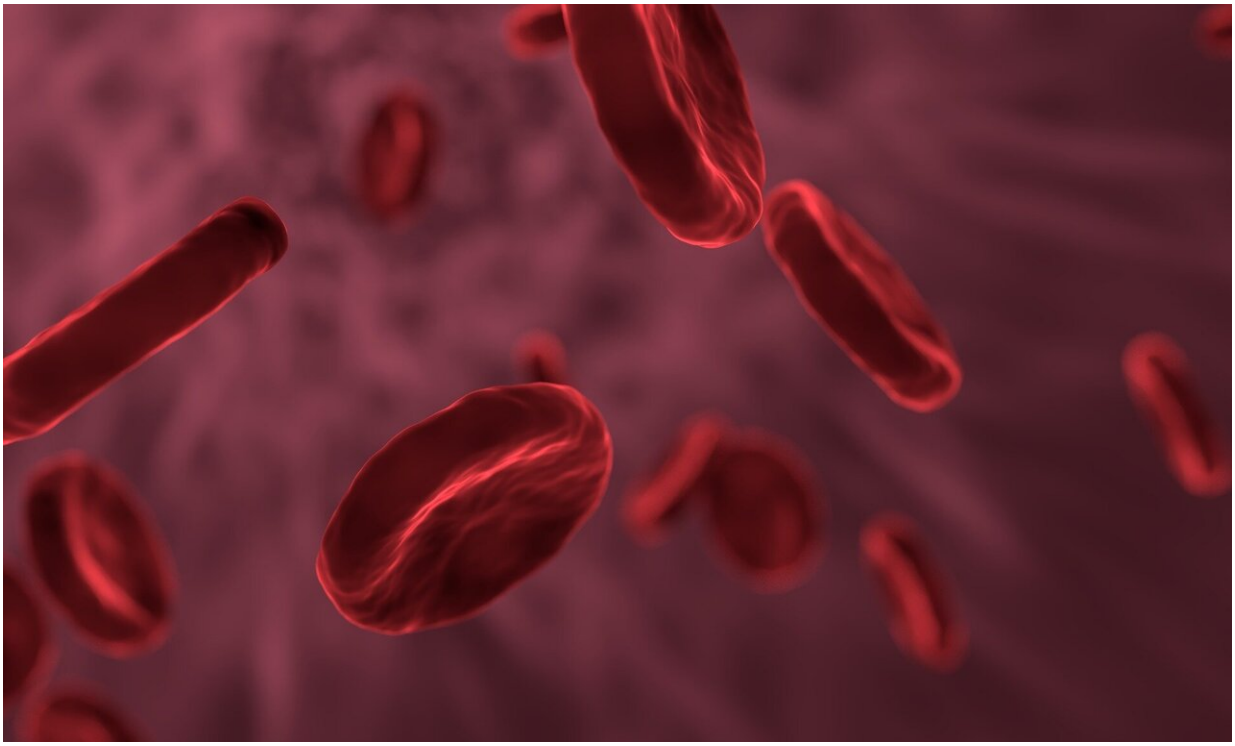

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The cells of a subset of myeloproliferative neoplasms (MPNs), slow-growing blood cancers, have frameshift mutations in their calreticulin (CALR) gene that are associated with the disease. The tail end of this gene's mutated protein product ($CALR^{MUT}$) should be an ideal neoantigen. Yet T cells directed against the $CALR^{MUT}$ fragment are

rarely found in MPN patients. To figure out why, Ludwig MSK's Taha Merghoub and his colleagues examined the class I MHC genes—which present antigens to T cells—of patients with this kind of MPN.

When T cells see these antigens, they are activated and kill the cells that express them. Merghoub and his colleagues found that these patients tend to lack MHC-I proteins that bind strongly to $CALR^{MUT}$ neoantigens, which may explain why their mutant cells aren't eliminated by the immune system before they can cause MPNs. The researchers generated mutant versions of $CALR^{MUT}$ peptides that bind efficiently to the MHC-I proteins found in these patients but retain the sequences that are recognized by T cell receptors.

These so-called "heteroclitic" peptides, they reported in a paper in *Science Translational Medicine*, elicited a cross-reactive CD8+ T cell response to $CALR^{MUT}$ in human blood samples, while the original peptides did not. The researchers verified these findings in mice as well. Taha and his team suggest on the basis of these studies that heteroclitic peptide-based cancer vaccines might represent a promising therapeutic approach for $CALR^{MUT}$ MPN patients.

More information: Mathieu Gigoux et al, Calreticulin mutant myeloproliferative neoplasms induce MHC-I skewing, which can be overcome by an optimized peptide cancer vaccine, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.aba4380

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