Novel biomimetic polypeptides activate tumor-infiltrating macrophages, offering hope for cancer therapy

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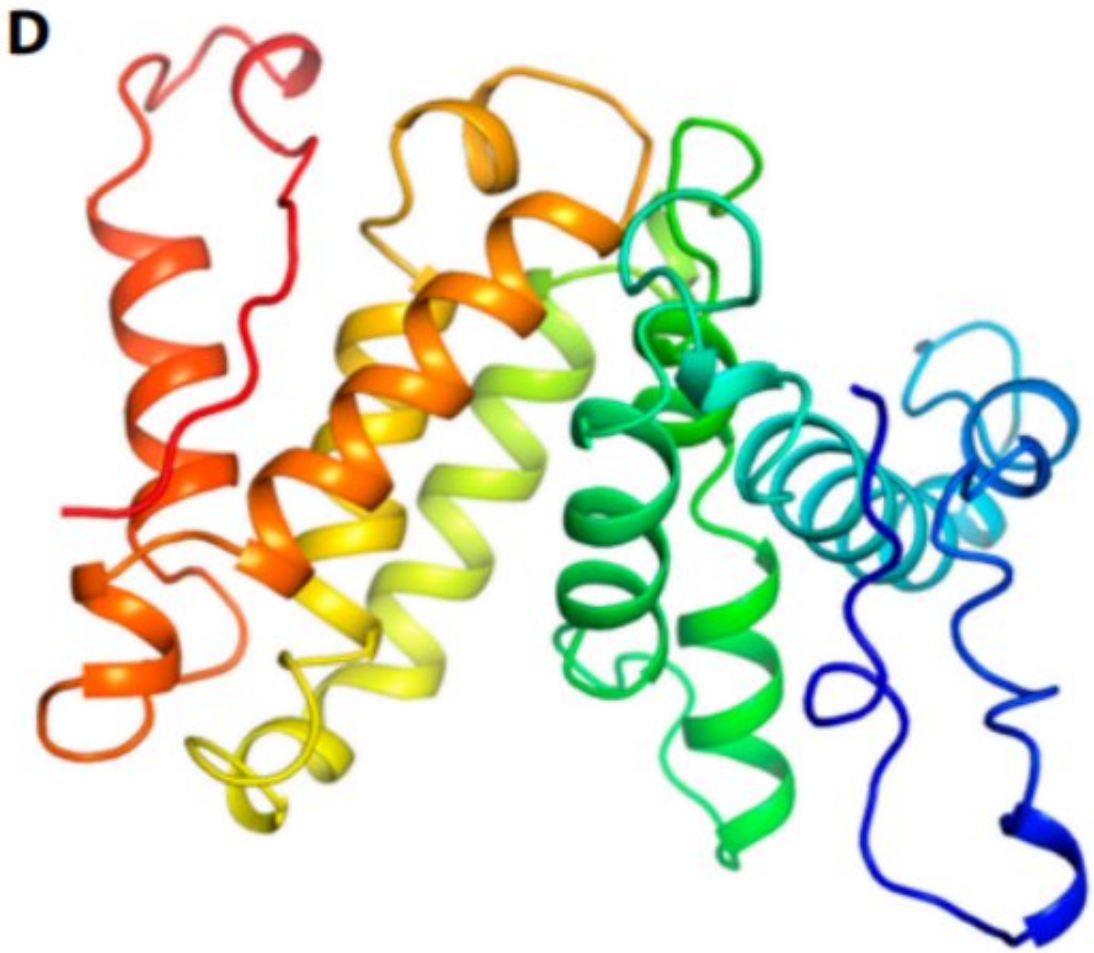

The tFold-predicted protein structure of a BMPP comprising (GGSGGPGGGPASAAANSASRATSNSP)n, the RGD motif from collagen and the IKVAV motif from laminin, designed by a research team from China.

BMPPs can activate the M1 phenotype of macrophages, which can be used for immunotherapy against cancer. Credit: Na Kong from ShanghaiTech University

Macrophages are highly specialized cells of the immune system that help the body detect and fight deadly pathogens. In particular, M1-like macrophages detect and destroy tumor cells, and release protective chemokines such as interleukin (IL)-6 and tumor-necrosis factor α (TNF α), thus shielding the body from life-threatening pathologies like cancer.

However, not all macrophages show anti-tumor potential. Certain types of macrophages, i.e., M2-like macrophages, promote tumor growth. Luckily, the desired macrophage phenotype—a set of traits resulting from the genetic makeup of the macrophage—can be activated by modulating the physiological microenvironment of the cells. Interestingly, multiple nanomaterial-based immunomodulators have been developed in the past, which are known to facilitate the phenotype transition of macrophages from M0 to M1.

Recently, a team of researchers led by Dr. Na Kong and Dr. Yuan Yao from the ShanghaiTech University, China, conducted a study to design novel immunomodulators—biomimetic polypeptides (BMPPs)—that could activate tumor-infiltrating macrophages, i.e., M1-like macrophages. Their study was published in *BioDesign Research*.

Elaborating on the development of BMPPs, Dr. Yao remarks, "Combining de novo protein design and biosynthesis techniques, we designed a BMPP self-assembled nano-immunomodulator to trigger the activation of a specific macrophage phenotype. It was intended to be made up of (GGSGGPGGGPASAAANSASRATSNSP)n, the RGD motif from collagen, and the IKVAV motif from laminin."

It is important to note, that previously developed nano-immunomodulators exhibited clear limitations, such as biotoxicity and low biocompatibility.

To overcome such limitations, Dr. Yao and team tried a unique approach. They designed and biosynthesized a biomimetic nanofibril—a highly ordered and stable structure comprising self-assembled repetitive building blocks. To do so, they validated the predicted monomers and higher-order complexes using molecular dynamics simulations—computational studies used to mimic the movement of atoms, molecules, or even large biomolecules such as polypeptides and proteins.

The resultant BMPPs specifically harbored the RGD and IKVAV motifs—small nature-conserved regions from proteins—because prior studies have shown that these motifs contain amino acid residues with putative immunomodulatory capabilities.

Following biosynthesis, the team conducted a variety of assays including enzyme-linked immunosorbent assay (ELISA), to test the efficacy of the newly biosynthesized BMPPs. Cell proliferation assays conducted using RAW264.7 cells demonstrated the general biosafety and cytocompatibility of BMPPs. Moreover, results from ELISA revealed that BMPP nano-immunomodulators increased the protein expression levels of IL-6 and TNFα, without affecting the expression levels of IL-10.

This clearly demonstrated that M1 macrophage polarization occurred at high BMPP concentrations and that BMPP nano-immunomodulators were presumably activating the M1-like macrophages.

"Unlike metal or synthetic polymer-based nanoparticles, these BMPPs exhibit excellent biocompatibility, high efficacy, and precise tunability in immunomodulatory effectiveness. With such encouraging findings,

we are motivated to continue our research into cancer immunotherapy applications," says Dr. Yao.

More information: Na Kong et al, De Novo Design and Synthesis of Polypeptide Immunomodulators for Resetting Macrophage Polarization, *BioDesign Research* (2023). DOI: 10.34133/bdr.0006

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