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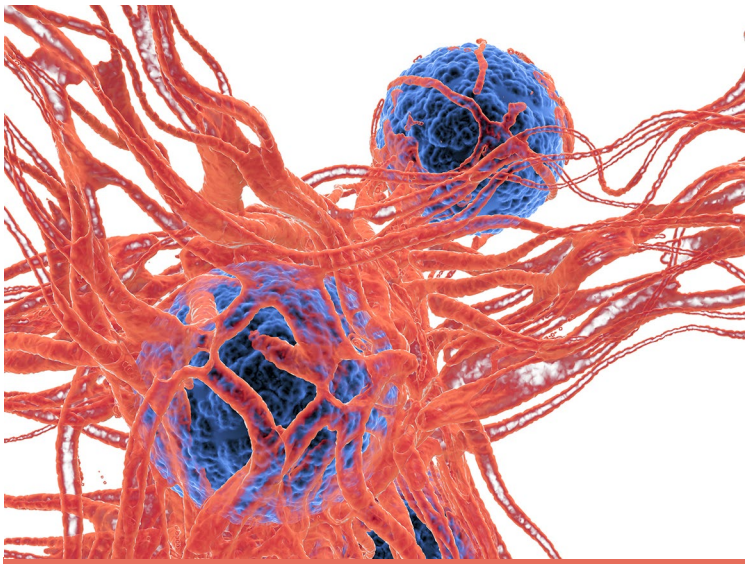

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IMMUNOENGINEERING

Cutting ties

> Shielding the peptide inside nanoparticles prevents the binding of blood components and protects the peptide from clearance

The formation of new blood vessels is a major cause of tumour regrowth after chemotherapy. Neoangiogenesis is facilitated by macrophages, recruited to the tumour site during treatment, and by endothelial cells in the tumour microenvironment, which both bind angiopoietin — a vascular growth factor. Now, writing in *ACS Nano*, Guangjun Nie, Ying Zhao, Zhihai Qin and colleagues report a peptide nanoparticle that binds to the angiopoietin receptor on macrophages and endothelial cells and inhibits tumour blood vessel formation. Treatment with the nanoparticles in combination with chemotherapy prevents cancer relapse and metastasis in a triple-negative breast cancer mouse model.

Binding of angiopoietin to tyrosine kinase with immunoglobulin and epidermal growth factor homology 2 (Tie2) — a receptor overexpressed on tumour-associated macrophages and endothelial cells — triggers the formation of new tumour vessels. Peptides that bind to Tie2 can be used to block this signalling pathway, which prevents angiogenesis and thus cuts cancer cells off from nutrient supply. "The T4 peptide has previously been shown to bind to Tie2 and disrupt the angiopoietin/Tie2 signalling pathway, which blocks tumour growth," explains Nie. "However, peptide therapeutics are limited by low bioavailability, enzymatic degradation and a short circulation half-life."

To address these limitations, the researchers designed a dual-responsive amphiphilic peptide that self-assembles into nanoparticles at physiological pH. The peptide contains the T4 sequence, a cleavage site for legumain, which is a protease overexpressed in tumour cells, a hydrophilic sequence to prolong the blood circulation time and the hydrophobic molecule diethylaminopropyl isothiocyanate (DEAP). DEAP is protonated at pH 6.7–7.1, which is the characteristic pH range of a tumour microenvironment. Protonation of DEAP leads to swelling of the nanoparticles and thus exposure of the protease cleavage site. Enzymatic processing then causes the release of the T4 peptide.

"Shielding the peptide inside nanoparticles prevents the binding of blood components and protects the peptide from clearance," comments Nie. "Thereby, we can increase the half-life and bioavailability of the peptide, while maintaining its activity until delivery to the tumour site." Upon arrival at the tumour microenvironment, the combination of pH sensitivity and enzymatic processing causes the release of the peptide from the nanoparticles and subsequent blocking of the Tie2 receptor on macrophages and endothelial cells, which leads to a decrease in macrophage viability and prevents the formation of endothelial tubules.

The researchers demonstrated that chemotherapy followed by intravenous injection of the nanoparticles prevents tumour recurrence in a triple-negative breast cancer mouse model. Furthermore, the number of metastatic foci in the lung — typical for triple-negative breast cancer — could be substantially decreased.

However, the nanoparticles also accumulate in the liver, spleen and kidneys and, therefore, the researchers are currently investigating potential long-term side effects of the particles. Moreover, based on the efficacy of the nanoparticle platform for breast cancer, they also plan to test the Tie2-inhibiting nanoparticles for other tumour types, characterized by a high degree of malignancy and tumour recurrence.

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ORIGINAL ARTICLE Zhang, L. et al. Cooperatively responsive peptide nanotherapeutic that regulates angiopoietin receptor Tie2 activity in tumor microenvironment to prevent breast tumor relapse after chemotherapy. *ACS Nano* https://doi.org/10.1021/acsnano.8b08142 (2019)