Researchers hack the metastatic process using nanoparticles

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Memorial Sloan Kettering Cancer Center (MSK) molecular pharmacologist Daniel Heller, PhD, and colleagues have identified a new strategy to target drugs specifically to cancer sites, including metastatic tumors. The approach involves nanoparticles designed to mimic a mechanism that tumors themselves use to metastasize throughout the body. This work, which will be featured on the cover of the June 29 issue of *Science Translational Medicine*, was applicable across a wide range of tumor and drug types and can potentially be applied to other conditions including vascular and autoimmune diseases.

Metastatic tumors, the cause of roughly 90 percent of cancer deaths, have long evaded effective treatments. One major reason is that most cancer drugs never accumulate in large enough amounts at the tumor site. Additionally, they have been known to cause side effects due to their activity in healthy tissues. "The ability to target drugs specifically to metastatic tumors would greatly improve their effectiveness," said Yosi Shamay, lead author of the article and a member of Dr. Heller's lab.

Dr. Heller and colleagues targeted P-selectin, a molecule that appears on the inner walls of blood vessels and aids in the formation of metastases. To metastasize, cancer cells leave the primary tumor and circulate in the blood. In certain sites, these cells can stick to P-selectin to stop circulating, leading them to exit the blood vessel and form a new tumor. By targeting P-selectin, Dr. Heller and colleagues discovered a way to hack into the mechanism that cancer cells use to metastasize.

To use P-selectin to target metastatic cancers, they developed nanoparticles—tiny particles with diameters one-thousandth the width of a human hair—composed of fucoidan, a polysaccharide extracted from brown algae that binds to P-selectin. The nanoparticles were filled with different cancer drugs, including chemotherapeutics and newer precision medicines.

The researchers conducted experiments showing that the nanoparticles targeted cancer sites including metastatic tumors in the lungs of experimental metastasis models. "We found that the nanoparticles were more effective than the drugs normally were, they allowed the administration of lower drug doses, and they reduced side effects," Dr. Heller said.

In collaboration with the laboratories of José Baselga and Maurizio Scaltriti at MSK, the researchers filled the nanoparticles with a personalized drug—an MEK inhibitor that acts on cancers with specific mutations. These nanoparticles were much more effective than the drug without the particle, allowing the drug dose to be reduced by more than 85 percent while avoiding side effects in the skin. "Personalized medicines have great potential in cancer treatment," Dr. Heller said, "but these new drugs often have side effects that could be mitigated by directing them to the disease sites."

The researchers also found that they could target the nanoparticles to tumors that didn't even have the target molecule, P-selectin. Radiotherapy, it turns out, causes P-selectin to show up in the tumor site. In collaboration with MSK radiation biologist Adriana Haimovitz-Friedman, PhD, the researchers found they could use radiation to trigger the expression of P-selectin and "guide" the nanoparticles to the cancer site. Low doses of radiation can be accurately delivered selectively to tumors while sparing surrounding non-malignant tissues, essentially allowing researchers to create their own target when necessary. "Radiation-guided drug delivery might allow us to target drugs to nearly any site in the body," Dr. Haimovitz-Friedman said.

While this study demonstrates a clear therapeutic

benefit using drug-encapsulated P-selectin particles, compared to passively targeted drug carriers or a fucoidan polymer control, further in-depth studies are needed, including clinical trials, to bring this technology to the bedside.

More information: Y. Shamay et al. P-selectin is a nanotherapeutic delivery target in the tumor microenvironment, *Science Translational Medicine* (2016). DOI: 10.1126/scitranslmed.aaf7374

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