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Scientists find new mechanism behind resistance to cancer treatment

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Developing resistance to chemotherapy is a nearly universal, ultimately lethal consequence for cancer patients with solid tumors – such as those of the breast, prostate, lung and colon – that have metastasized, or spread, throughout the body. A team of scientists led by Fred Hutchinson Cancer Research Center has discovered a key factor that drives this drug resistance – information that ultimately may be used to improve the effectiveness of therapy and buy precious time for patients with advanced cancer. They describe their findings online Aug. 5 in advance of print publication in *Nature Medicine.*

"Cancer cells inside the body live in a very complex environment or neighborhood. Where the tumor cell resides and who its neighbors are influence its response and resistance to therapy," said senior author Peter S. Nelson, M.D., a member of the Hutchinson Center's Human Biology Division.

Nelson and colleagues found that a type of normal, noncancerous cell that lives in cancer's neighborhood – the fibroblast – when exposed to chemotherapy sustains DNA damage that drives the production of a broad spectrum of growth factors that stimulate cancer growth. Under normal circumstances, fibroblasts help maintain the structural integrity of connective tissue, and they play a critical role in wound healing and collagen production.

Specifically, the researchers found that DNA-damaging cancer treatment coaxes fibroblasts to crank out a protein called WNT16B within the

tumor neighborhood, or microenvironment, and that high levels of this protein enable cancer cells to grow, invade surrounding tissue and resist chemotherapy.

The researchers observed up to 30-fold increases in WNT production – a finding that was "completely unexpected," Nelson said. The WNT family of genes and proteins plays an important role in normal development and also in the development of some cancers but, until now, was not known to play a significant role in treatment resistance.

This discovery suggests that finding a way to block this treatment response in the tumor microenvironment may improve the effectiveness of therapy.

"Cancer therapies are increasingly evolving to be very specific, targeting key molecular engines that drive the cancer rather than more generic vulnerabilities, such as damaging DNA. Our findings indicate that the tumor microenvironment also can influence the success or failure of these more precise therapies." In other words, the same cancer cell, when exposed to different "neighborhoods," may have very different responses to treatment.

The major clinical reason that chemotherapy ultimately fails in the face of advanced cancer, Nelson said, is because the doses necessary to thoroughly wipe out the cancer would also be lethal to the patient. "In the laboratory we can 'cure' most any cancer simply by giving very high doses of toxic therapies to cancer cells in a petri dish. However, in people, these high doses would not only kill the cancer cells but also normal cells and the host." Therefore, treatments for common solid tumors are given in smaller doses and in cycles, or intervals, to allow the normal cells to recover. This approach may not eradicate all of the tumor cells, and those that survive can evolve to become resistant to subsequent rounds of anti-cancer therapy.

For the study the team of researchers – which also involved investigators at the University of Washington, Oregon Health and Science University, the Buck Institute for Research on Aging, the Lawrence Berkeley National Laboratory – examined cancer cells from prostate, breast and ovarian cancer patients who had been treated with chemotherapy.

"This study is an example of collaborative, translational research that capitalizes on years of federally funded investments into the development of tissue banks and clinical trials in which we were able to track long-term patient outcomes. Investing in this type of infrastructure is critical but may take many years to see payoff," said Nelson, who serves as principal investigator of the Pacific Northwest Prostate Cancer SPORE, a federally funded, multi-institution research consortium led by the Hutchinson Center.

More information: "Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B," *Nature Medicine*, DOI:10.1038/nm.2890

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