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Melanoma stem cells' evasive talents

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Melanoma, if not detected in its early stages, transforms into a highly deadly, treatment-resistant cancer. Although the immune system initially responds to melanoma and mounts anti-tumor attacks, these assaults are generally ineffective, allowing more advanced melanomas to win the battle and spread beyond the primary site. Now, researchers at Children's Hospital Boston and Brigham and Women's Hospital (BWH) shed light on how melanomas stimulate, yet ultimately evade, a patient's immune system. Their work, published online January 12 by the journal *Cancer Research,* also suggests ways drugs might block these tactics.

In 2008, the same team, led by Markus Frank, MD, of the Transplantation Research Center of Children's and BWH, and George Murphy, MD, chief of Dermatopathology at BWH, showed in the journal Nature that a key reason for melanoma virulence is a small group of tumor stem cells that are able to grow despite chemotherapy drugs, allowing the tumor to re-grow and progress. They also showed that targeting these cells (identifiable by a molecule on their surface known as ABCB5) could successfully inhibit tumor growth in mice. (The ABCB5 technology has been licensed and is currently in clinical drug development.)

In their new paper, first author Tobias Schatton, PhD, of the Transplantation Research Center, and colleagues show that these ABCB5-positive cells also produce molecules that inhibit the body's natural immune attack, known as PD-1 and B7.2. These molecules work, they found, by triggering white blood cells known as regulatory T cells (T-regs), to dampen the normal anti-melanoma response. The T-regs are

thus tricked into protecting the deadly melanoma stem cells from the body's own defenses.

"To my knowledge, this study provides the first evidence that cancer stem cells escape and down-regulate host antitumor immunity," says Frank, the study's senior investigator, also affiliated with the Department of Dermatology at BWH. "This might have important implications for cancer therapy, especially in malignant melanoma."

Additional experiments showed that melanoma stem cells stimulate surrounding cells' production of IL-10, a signaling molecule that suppresses the immune system, and inhibit production of IL-2, which stimulates immune attack. The melanoma stem cells also produce fewer of the antigens that trigger immune responses, further evading immune attack.

The study adds to a growing body of evidence that melanoma stem cells have developed a repertoire of complementary strategies to outsmart host defenses, camouflaging them from the very immune cells and therapeutic agents that seek to destroy them. It also suggests new strategies for attacking the deadly skin cancer.

"Melanoma stem cell targeting holds promise for an absolute cure, because you're hitting the cells that really matter - the cells that drive tumor progression," says Murphy. "By understanding the precise molecular pathways whereby melanoma stem cells cajole the immune system into a permissive role, scientists are now closer to identifying ways of blocking or inhibiting such tactics."

For example, inhibition of PD-1 and B7.2 on melanoma stem cells could render them vulnerable not only to immune defenses, but also to treatments that are currently only effective against the more susceptible non-stem cell component of the tumor. Stripping away the stem cells'

"protective shield" may allow a tumor to be killed without the possibility of it re-growing.

Melanomas are highly immunogenic cancers, initially provoking anti-tumor attacks, as evidenced by patients whose brown-black skin tumors seem to have partly dissolved away, producing regions of pink to white coloration where pigment previously existed. But ultimately, melanomas evade the immune system; until now, how the key cells that drive the melanomas' growth accomplish this has been a mystery.

The current work is relevant primarily to metastatic melanoma, which is often incurable, says Murphy. In their early, flat stages, melanomas can be cured surgically, but are potentially deadly once they grow as a skin elevation (sometimes no larger than a small pea) and spread to lymph nodes or vital organs. Scientists have long sought to find ways to target and destroy melanoma deposits that have already spread.

The research team is now planning to examine the ability of currently approved or investigational immunotherapeutic strategies to target and inhibit the immune-evasion tactics and immunological tolerance induced by melanoma stem cells. Specifically, they hope to participate in several ongoing or future clinical trials that target specific immunologic signaling pathways in melanoma patients (using anti-PD-1 antibodies, for example), to track the response of ABCB5-positive melanoma stem cells.

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