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Popular cancer drug target implicated in cardiovascular defects

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UNC School of Medicine researchers have discovered an unlikely relationship between CXCR7 – a protein implicated in tumor growth and metastasis – and adrenomedullin – a hormone involved in cardiovascular health. Deleting CXCR7 allows adrenomedullin to run rampant, triggering the development of an enlarged heart and the overgrowth of the lymphatic vessels that traffic immune cells and fluids throughout the body.

The study, published September 8 in the journal *Developmental Cell*, reveals that CXCR7 binds to the ligand adrenomedullin. The UNC research suggests that this relationship is important because CXCR7 has become a popular candidate for cancer-drug developers. The UNC paper also provides a novel and unexpected role for CXCR7 in lymphatic vessels, which are largely understudied, but play critical roles in inflammation, edema, and tumor metastasis.

"Our results suggest that inhibiting CXCR7 with a drug is also likely to influence the adrenomedullin peptide and may unexpectedly and negatively affect lymphatic vessels," said senior study author Kathleen M. Caron, PhD, professor and chair of the department of cell biology and physiology. "Lymphatic vessels can function as highway conduits for the spread of cancer cells through the body, so being aware of how a potential drug might influence the function of these vessels is critically important."

Most receptor proteins act like molecular mailboxes that sit on the

surface of the cell; they take in signaling molecules from nearby tissues and then transmit their messages into the cell, where specific commands are carried out, such as helping fight an infection or spurring tumor growth.

CXCR7 is different. It's part of a rare class of proteins known as decoy receptors, which look like typical molecular mailboxes on the surface, but rather than transmitting messages, they chew them up like a trash compactor would. These decoy receptors destroy any excess signaling molecules in order to keep biological processes like inflammation and tissue development in check.

In 2007, several groups of biologists around the world began to knock out the CXCR7 gene in mice to try to understand its function. Because the CXCR7 gene is "turned on" in lymphocytes – a type of white blood cell – researchers expected the mice to have defects in their B and T cells, which would result in an underperforming immune system. Instead, the researchers discovered that the mutant mice had severe heart and valve defects and died shortly after birth.

Caron had previously seen the same defects in mouse models that contained three times the normal amount of the protein adrenomedullin. She began to contemplate the possible relationship between CXCR7 and adrenomedullin. Caron remembered literature from the 1990's that had suggested a link between the two. Back then, CXCR7 was going by another name – RDC1 – so it wasn't surprising to Caron that other researchers might not have made the same connection.

"One of the fun things about being in a field for a long time is you carry this historical literature with you," said Caron, a member of the UNC Lineberger Comprehensive Cancer Center and the UNC McAllister Heart Institute. "I remembered that RDC1 was once thought to be an adrenomedullin receptor, and so we put together the pieces from that

paper and the more recent findings to address a new and unexpected hypothesis."

Caron asked Klara Klein, a graduate student in her laboratory, to help prove the connection once and for all. First, Klein performed a biochemistry experiment to show that the CXCR7 decoy receptor would bind and destroy the adrenomedullin peptide. Klein took cultured cells, made sure that they expressed the CXCR7 receptor, and then added adrenomedullin. She took out samples of the media at different times, measured the amount of adrenomedullin, and then calculated how much of the peptide was left. Klein found that the adrenomedullin was gradually depleted over time. In contrast, when she added the peptide to cells that didn't express the CXCR7 receptor, the levels of adrenomedullin remained the same.

Klein then obtained a litter of CXCR7 mutant mice and confirmed that they did in fact have enlarged hearts. She also discovered that the mice had an overgrowth of lymphatic vessels. This made sense, if excessive adrenomedullin was implicated.

"The fact that these two types of mice had nearly identical effects suggested that adrenomedullin may be more than just another signal-triggering molecule," Caron said. "It may be the CXCR7 receptor's number one binding target." Klein and Caron thought that if the main role of CXCR7 was to control the amount of adrenomedullin, then they should be able to reverse cardiovascular defects by reducing the amount of adrenomedullin. To do so, they mated the CXCR7 knockout mice with mice that had half the normal amounts of adrenomedullin. Caron's team found that mice progeny had normal-sized hearts, and the lymphatic vessels of the mice were not overgrown.

"When you get rid of the CXCR7 receptor, you're essentially getting rid of the brake that slows down adrenomedullin's effects," Caron said. "If

they don't have the brake, but at the same time you lay off the gas, then you normalize the size of the heart and lymphatic vasculature."

Caron, who has had a long-term interest in the role of adrenomedullin in pregnancy, now wants to see how CXCR7 controls the dosing of this hormone in the placenta.

She previously showed that adrenomedullin is responsible for recruiting the mother's immune cells that infiltrate the placenta. Because dysregulation of the immune system during pregnancy underlies the majority of pregnancy complications – such as preeclampsia, preterm birth, and spontaneous abortion – understanding the role of the receptor in charge of tempering that innate immune response could lead to her lab's next big breakthrough.

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