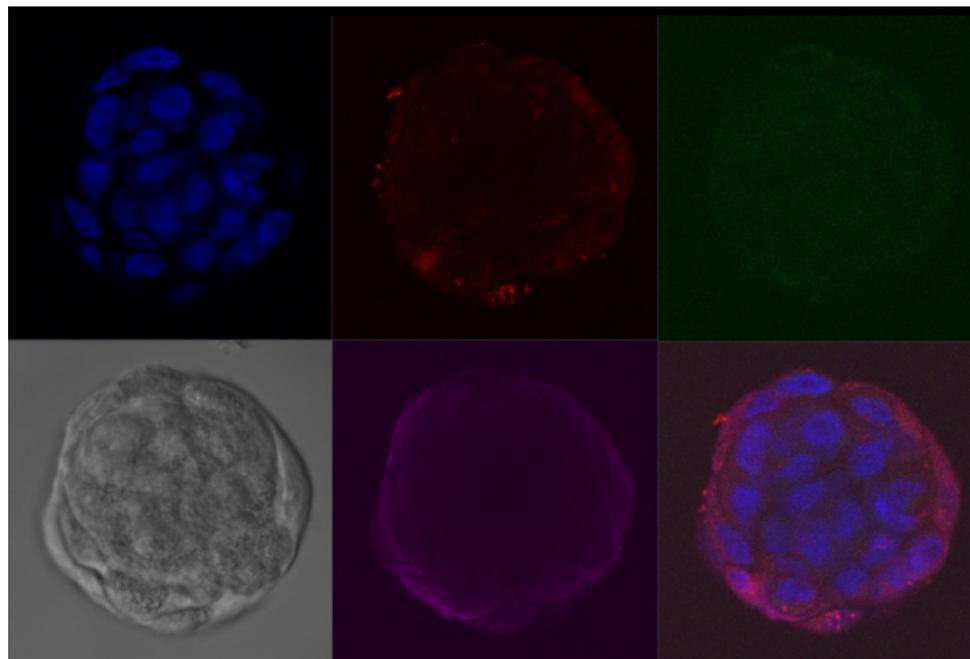


Peptidylarginine deiminases (PADIs) are post-translational modification enzymes that convert positively charged arginine or methylarginine residues on specific target proteins into citrulline, an uncharged, nonstandard amino acid. This activity, called citrullination, results in a net loss of positive charge, and thus has the potential to drastically change the structure, function, and interactions of the targeted protein.

The most widely-expressed PADI enzyme, PADI2, is thought to have an important role in the progression of several of the most common types of breast cancer from benign hyperplasias to malignant tumors. Although the exact functions of PADI2 are unknown, one clue to how it may promote cancer progression comes from the fact that it acts on interleukin 8 (CXCL8), a signaling molecule that promotes inflammation. Inflammation has long been recognized to have a curious and often paradoxical role in cancer development. The key functions of CXCL8, specifically, are to promote growth of new blood vessels, promote cell survival and growth, and to attract neutrophils - the “seek-and-destroy” infantrymen of the immune systems - out of the bloodstream and into inflamed tissue. Normally, CXCL8 is secreted in a partially active form, and then cleaved to produce CXCL8 in its truncated and fully active form. Only this truncated form is capable of recruiting neutrophils from the bloodstream. How-

ever, citrullination of CXCL8 by PADI2 at the site of cleavage prevents this truncation. This citrullinated, untruncated form is equally potent in promoting tissue growth, but it is no longer able to recruit neutrophils, thus spurring tumor growth while undermining an effective anti-tumor immune response. We plan to use in vitro tumor spheroids (in vivo-like aggregations of cells that can mimic the in vivo



tumor microenvironment relatively faithfully) to test whether there is a correlation between PADI2 activity, secretion of citrullinated and untruncated CXCL8, and

aggressive tumor growth. We will treat spheroids with a PADI inhibitor and then use immunocytochemistry, RT-qPCR, and western blots, combined with mass spectrometry to determine the citrullination and truncation status of secreted CXCL8, to shed light on how PADI activity affects tumor morphology, inflammatory state, and malignancy.

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This research will be conducted at Cornell University, in the lab of Prof. Scott Coonrod

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Investigating the role of interleukin 8 citrullination in breast cancer progression