Elusive receptor for progranulin found

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Progranulin is produced and secreted by most cells in the body. From skin to immune cells, brain to bone marrow cells, progranulin plays a key role in maintaining normal cellular function. In cancer, too much progranulin makes tumors (particularly prostate carcinomas) more aggressive and metastatic, whereas in neurodegenerative diseases, too little is associated with disease onset and progression. Until now, studying progranulin has been tricky as the receptor that communicates biological information to the cell's signaling machinery has remained elusive for decades. Now, researchers at Thomas Jefferson University's Sidney Kimmel Cancer Center discovered a cell-surface receptor highly expressed by cancerous and brain cells that directly and tightly binds progranulin. Importantly, the researchers also showed that this binding activates a cellular program that makes cancer cells more aggressive.

The results were published in *The Journal of Cell Biology*.

"Identifying the functional signaling receptor for progranulin will help us understand how this molecule functions in cancer and whether pharmacologically targeting it will slow the progression of a number of cancers," says Renato V. Iozzo, M.D., Ph.D., Gonzalo E. Aponte Professor and Deputy Chair of the Department of Pathology, Anatomy & Cell Biology at Thomas Jefferson University and researcher at the Sidney Kimmel Cancer Center at Jefferson. "It may also help researchers better understand the role of progranulin function and deficiency in neurodegenerative diseases including Parkinson's, Alzheimer's, and possibly even autism."

Using an array of unbiased biochemical and cellular approaches, the researchers demonstrated that Ephrin type-A receptor 2, or EphA2, bound tightly to progranulin. Following progranulin binding, key components of the intracellular signaling apparatus that are involved in both cancer-promoting and perhaps neurodegenerative processes known as Akt and Erk1/2, were rapidly activated. When EphA2 was blocked, however, these pathways did not activate. The researchers further showed that progranulin binding triggered a positive feed-forward loop, wholly dependent on EphA2 signaling that increased the secretion of progranulin from the cancer cell. Finally, when EphA2 was depleted from endothelial cells, progranulin failed to trigger the formation of new blood vessels, a process considered essential for progressive tumor growth and metastasis.

Researchers had previously identified other receptors with progranulin-binding abilities: sortilin and tumor necrosis factor receptor 1 and 2 (TNFR1/2). Sortilin is capable of binding progranulin outside the cell and internalizing it, while TNFR1/2 are receptors primarily involved in coordinating inflammatory responses. Recent reports had cast doubt as to whether these two candidate receptors were bona fide progranulin receptors. In one instance, changes in neuronal outgrowth were seen even when sortilin was absent and some evidence questioned whether TNFR1/2 could bind directly to progranulin at all.

Indeed, when Dr. Iozzo and colleagues removed sortilin from the cells expressing EphA2, they found that sortilin was not necessary for progranulin/EphA2 signaling. They found that cells lacking sortilin accumulate progranulin outside of the cell, and can therefore increase the bioavailability of progranulin to signal via EphA2 to augment more progranulin production. In pathological situations where progranulin levels are vital, understanding the mechanism of the progranulin/EphA2 feedback loop may prove key to disease development and progression.

"The discovery of EphA2 as a receptor for progranulin is somewhat unexpected, in part because it was commonly believed that Ephrin receptors only bound other members of the vast Ephrin family," said Dr. Iozzo. "This finding turns that expectation on its head, and offers new tools and concepts for exploring pathological, and homeostatic functions of progranulin."

More information: T Neill, et al., "EphA2 is a functional receptor for the growth factor progranulin." *J Cell Biol.* 2016.

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