Research finds new link between inflammation and cancer

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Virginia Commonwealth University Massey Cancer Center researchers have uncovered a new link between chronic inflammation and cancer. Although cancers do not always cause inflammation, chronic inflammation is known to help tumor cells grow.

In an article published in the June issue of *Nature*, VCU Massey scientists Sarah Spiegel, Ph.D., and Tomasz Kordula, Ph.D., and their co-authors examine how sphingosine-1-phosphate (S1P), a lipid mediator in the blood that influences immune cell circulation, also regulates inflammation and cancer. They reported that S1P is a missing cofactor that is required for the activity of TRAF2, the key regulator of NF-kappaB, which acts as a master on-off switch in controlling inflammation and cancer.

Spiegel, who is internationally recognized for her pioneering work on bioactive lipid signaling, discovered almost two decades ago that S1P is a potent lipid mediator that stimulates cell growth. S1P and the kinase that produces it, SphK1, have since emerged as critical regulators of numerous fundamental biological processes affecting health and disease.

"It is difficult to find an area of physiology and pathophysiology in which S1P does not have important if not key roles. Appropriate to its name, which is associated with the enigma of the Sphinx, how S1P so profoundly regulates cell fate decisions has long remained a mystery," said Spiegel, co-leader of VCU Massey's Cancer Cell Signaling Program and chair of VCU School of Medicine's Biochemistry and Molecular

Biology Department.

The puzzle of how such a simple molecule as S1P can have diverse roles has been solved by VCU Massey researchers' discovery that this lipid mediator functions not only as a "first messenger," a ligand or agonist that binds to specific cell surface receptors, but also inside the cells as an "intracellular second messenger" that is required for activation of the transcription factor NF-kappaB.

These findings also provide an explanation for the numerous observations of the importance of the enzyme that produces S1P, SphK1, in protection of cancer cells against chemotherapeutic drugs and the correlation of its levels with poor prognosis of many types of cancers, including breast, colorectal and brain.

Spiegel hopes that specific SphK1 inhibitors they are developing will pave the way for future potent and specific drugs that target SphK1 for the treatment of cancer.

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