Double drug combo could shut down abnormal blood vessel growth that feeds disease

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A new study by researchers at Weill Cornell Medical College shows combining two already-FDA approved drugs may offer a new and potent punch against diseases in which blood vessel growth is abnormal—such as cancer, diabetic retinopathy, macular degeneration and rheumatoid arthritis.

Their study, published in the Sept. 11 issue of the journal *Developmental Cell*, is the first to show that a protein, sphingosine 1-phosphate receptor-1 (S1P1), is a key player in angiogenesis—the growth process of new blood vessels in the body from pre-existing vessels. S1P1, previously known to modulate immune system function, is the target of the approved drug fingolimod used to treat the autoimmune neurological disease multiple sclerosis.

Researchers have discovered that S1P1 works hand-in-hand with vascular endothelial growth factor (VEGF), which stimulates blood vessel growth. VEGF is the target of a number of different cancer drugs that have not proven to be as effective as originally envisioned in shutting down the excess blood vessels that provide nutrients to growing tumors and other diseases that rely on extra blood supply.

"The body needs to make new blood vessels that transport oxygen and blood. We now know that VEGF starts the process of sprouting new blood vessels from existing vessels, and S1P1 finishes it," says Dr. Timothy Hla, professor of pathology and laboratory medicine and director of the Center for Vascular Biology at Weill Cornell.

"Angiogenesis is abnormal in many diseases; by targeting both S1P1 and VEGF, it may be more effective to strike out disease than using just VEGF inhibitors alone," he says.

Not only are VEGF inhibitors currently used to treat cancer, these drugs are also used to block excessive angiogenesis in the eyes of diabetics and vascular proliferation that occurs in the wet form of age-related macular degeneration. "We are intrigued to see what the potential for treating these eye diseases would be if S1P1 axis was also targeted," Dr. Hla says.

In rheumatoid arthritis, which is driven by reactive and inflammatory immune cells, a S1P1 inhibitor could block both immune and blood vessel-related mechanisms, and therefore may be beneficial, based on the study's findings. In addition, Dr. Hla points out that while the existing approved S1P1 inhibitor fingolimod has had some adverse effects in some multiple sclerosis patients, there are new inhibitors of S1P1 being developed by many companies that could also be tested in combination with a VEGF inhibitor for treating these diseases.

An Antenna that Senses Blood Flow

Angiogenesis is needed for many normal tissue growth, repair and regenerative processes, which ultimately results in increased blood flow and oxygenation of tissues.

The Hla laboratory has long been interested in defining the molecular mechanisms of the angiogenic process, in which endothelial cells from pre-existing blood vessels sprout, move and then change to form new vascular channels. Dr. Hla was first to identify S1P1 as a key angiogenic response gene, and he also successfully cloned and characterized the receptor.

In this study, the research team shows that as new blood vessel networks form, the resulting blood flow activates S1P1 on the surface of endothelial cells and relays signals inside these cells to stabilize

new blood vessel networks.

"The S1P1 molecule acts like an antenna to sense blood flow. If blood flow is reduced, then normal S1P1 signaling is interrupted, destabilizing blood vessel formation, causing the endothelium to undergo an inflammatory process," Dr. Hla says. "This happens in many diseases with abnormal vessels, including rheumatoid arthritis, psoriasis and even cancer."

In their laboratory studies, the researchers found that blocking S1P1 resulted in abnormal endothelial function and blood vessel growth. Inhibiting S1P1 causes new vessels to leak and become unstable. Blocking S1P1 would be beneficial, for example, to cut off the blood supply feeding a cancerous tumor, researchers report.

"This research defines one of the fundamental mechanisms of blood vessel growth that is vital to normal health and that also fuels many diseases," he says. "This research could ultimately lead to our ability to better modulate blood vessel health and growth, especially in diseases that depend on extra blood to sustain them."

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