Dual-action protein developed better restricts blood vessel formation

August 9 2011, By Andrew Myers

(Medical Xpress) -- Cancer needs blood. In fact, some cancer medications work solely to slow or prevent cancer cells from creating new capillaries, choking off their much-needed blood and nutrient supply to halt the growth of tumors.

In a paper published online Aug. 8 in the Proceedings of the National Academy of Sciences, researchers at Stanford University describe the creation of a new type of engineered protein that is significantly more effective at preventing the formation of blood vessels by targeting not one, but two of the chemical receptors that control the creation of new capillaries - a process known as angiogenesis. The study shows that the new protein blocks both receptors.

"Chemical receptors and their protein ligands control many cellular functions, but the protein must fit the receptor exactly. It's like a molecular jigsaw puzzle," said lead researcher Jennifer Cochran, PhD, assistant professor of bioengineering. "When the right proteins come along and engage their matching receptors, things begin to happen at the cellular level. In this case, we looked at the chemical signaling and cellular machinery responsible for producing new blood vessels."

Existing cancer treatments block the activity of specific receptors that control capillary creation. Some of these drugs act like a cork in a bottle, occupying the receptor and thus preventing capillary-inducing proteins from activating cell signaling and biochemical processes, while others attach to the capillary-inducing proteins and shield the receptor from

them.

Complicating matters for cancer researchers, however, is the fact that angiogenesis is often controlled by multiple receptors working together. "Cell-signaling pathways are analogous to a safe-deposit box requiring many keys to open," said Cochran.

In such situations, receptors work in tandem, communicating back and forth in a chemical collaboration known as cross-talk. Current anti-angiogenesis therapies, however, are able to target only single receptors. Thus, significantly limiting capillary growth requires blocking more than one receptor.

Cochran's team — including postdoctoral scholars Niv Papo, PhD, Adam Silverman, PhD, and Jennifer Lahti, PhD, who was a graduate student at the time of the research — identified likely pairs of collaborating receptors. They knew from a body of earlier research that there was significant cross-talk between two specific angiogenic receptors. Their goal was to create a single protein that could block both.

First, the team selected a protein that bonds with one of the receptors. Using it as a molecular "scaffold" they affixed, or substituted, a new section that could bond with the second receptor, all without altering the original function or the physical structure of the larger scaffold protein. They succeeded; their new protein blocks both receptors.

When delivered in a nutrient-rich matrix and implanted in mice, the Stanford protein showed dramatic ability to halt the creation of new capillaries. "Samples treated with our dual-action protein have minimal blood vessel formation, similar to a sample in which angiogenic factors are absent," Cochran said. "Importantly, this engineered protein more strongly inhibits angiogenic processes compared to single-receptor blockers."

Some researchers have suggested that the same result might be accomplished more easily with a cocktail of drugs, each targeting a specific receptor. Cochran acknowledged the feasibility of such approaches, but pointed out that each drug in the cocktail would require clinical trials and the approval of the U.S. Food and Drug Administration. The new protein could be the basis for one drug.

"This is a major advantage of two-in-one molecules," said Cochran. "A single FDA-approval process could possibly shave years off the development process, and there are obvious cost benefits to manufacturing only one drug instead of several. In addition, using state-of-the-art protein engineering methods that have been developed within the past decade or so, such molecules could be engineered for optimal therapeutic benefit while reducing unwanted side effects"

Beyond cancer, Cochran noted, the prevention of angiogenesis could prove helpful in the treatment of diseases such as macular degeneration, one form of which can lead to visual impairment or even blindness when unchecked capillaries grow in the retina.

As for the scaffolding approach, she said she sees a research strategy that might be applied to develop new, multifunctional proteins that work in other biomedical applications, from diagnostics and immunotherapy to tissue repair.

"All the attention being accorded dual-action proteins is warranted," Cochran said. "Sometimes, two are better than one."

Provided by Stanford University Medical Center