Discovery of natural compounds that could slow blood vessel growth

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Using computer models and live cell experiments, biomedical engineers at the Johns Hopkins University School of Medicine have discovered more than 100 human protein fragments that can slow or stop the growth of cells that make up new blood vessels.

Reporting online last week in the *Proceedings of the National Academy of Sciences,* the researchers say the findings could lead to developing treatments to fight diseases that depend on the growth of new blood vessels, including cancer, macular degeneration and rheumatoid arthritis.

"Before, there were only 40 known antiangiogenesis peptides," says Aleksander Popel, Ph.D., a professor of biomedical engineering at Hopkins. "Now, using a whole-genome, computer-based approach, we have identified more than 100 new ones, all of which can be further researched for their ability to fight the more than 30 known diseases affected by excessive blood vessel growth."

To identify short protein fragments — peptides — that can block blood vessel growth, the team started by looking at 40 known peptides that have been studied and characterized by other experts in the field to stop blood vessel growth in animal models of disease. Working under the assumption that the antivessel activity of these peptides can be attributed to similar features that are shared by a number of proteins, like the sequence of the peptide building blocks, the team first categorized the 40 known peptides by where they are located and what they look like.

Having defined nine families, the researchers then used computer programs and compared the peptide families to all of the proteins encoded by the genome. They found more than 120 peptides contained in 82 different proteins, many of which were not previously known to have any activity on blood vessel development.

"Computational methods only identify potential candidates," says Popel. "We next had to do the experiments on live cells to see if they had any real activity. Of the 82 proteins we identified, most were not previously known to have any antiangiogenic activity."

To test the activity of these candidate peptides, the researchers applied them to blood vessel cells growing in the lab and examined whether they had any effect on the growth, survival and movement of these cells. To test growth and survival, they added different amounts of peptide to dishes containing roughly 2,000 cells and after three days, counted how many cells were still alive.

To test cell movement, they placed cells in double-chambered dishes and treated the cells with a growth factor known to encourage cells to move. To some of the dishes they added the test peptides. After 20 hours, they measured the number of cells that had crawled from one chamber to the other. They then identified the protein receptors that the peptides bind to and were able to show in some cases that combinations of more than one peptide were better able to stop the cells than using single peptides.

"Basic, computational studies like this are critical to understanding normal blood vessel growth," says Popel. "A better understanding of normal growth gives us a better idea of what happens in disease."

The next step, Popel says, is to test these peptides in animal models of human disease and to identify the diseases most appropriately treated by these newly identified peptide inhibitors.

Source: Johns Hopkins Medical Institutions