

The Third Annual Evans Family Lecture in Pulmonary Medicine: Shaun R. Coughlin, M.D., Ph.D.

Thrombin Plus PARs Can Equal Vascular Disease



Two of the most devastating vascular diseases - heart attack and stroke - often share a similar cause. In both conditions, clots inside blood vessels prevent oxygen-rich blood from flowing to the body's vital organs, resulting in irreparable damage to the organs. Shaun R. Coughlin, M.D., Ph.D., Professor of Molecular and Cellular Pharmacology at the University of California, San Francisco, and Director of UCSF's Cardiovascular Research Institute, has taken pioneering steps toward discovering how these clots form and how to avert their formation in the future. Coughlin related his findings at the third annual Evans Family Lecture at Stanford University Medical Center.

A graduate of Massachusetts Institute of Technology and Harvard Medical School, Coughlin joined the UCSF medical faculty in 1986. He assumed his current roles of professor and director in 1997. Coughlin has received numerous awards in recognition of his work, including the Pasarow Foundation Award for Cardiovascular Research and the Basic Science Prize from the American Heart Association. He has published nearly 120 articles, reviews, and book chapters. Coughlin also serves on a number of scientific editorial and advisory boards.

At the outset of his lecture, Coughlin noted that he would tell two important tales about thrombin, a type of protease (catalytic enzyme) in blood that sets the coagulation process in motion. Coughlin's first story began with the formation of thrombin, which occurs when a hole develops in a vessel wall, allowing the blood inside the

vessel to seep out. The coagulation factors in the escaped blood then come into contact with tissue cells outside the vessel. The effect of this meeting, said Coughlin, is like putting a match to gasoline-and the fire that forms is thrombin.

Thrombin goes on to trigger a transformation in another protein called fibrinogen, resulting in a new protein known as fibrin, which serves as the primary culprit in blood clotting. Meanwhile, the remaining fibrinogen cells bind with platelets; this union also causes blood to clot. Together, fibrin and fibrinogen-platelet combinations produce clots that are often large enough to significantly obstruct blood flow through the vessels.

Coughlin pointed out that in this chain of events, thrombin "masquerades as a hormone," effecting a great deal of cellular change. How does a single protease set off such an intricate signaling network among cells? Coughlin found the answer in protease-activated receptors, or PARs - the long, string-like receptors that exist inside various blood cells.

In order for a cell to change, two cellular components must come together: a ligand (molecule) and a receptor. Once the ligand plugs into the receptor, the resulting combination directs the cell to change in certain ways, such as to form a new shape or bind to other cells. Before mingling with thrombin, a PAR is inactive, waiting for the right ligand to bind to its receptor. Thrombin changes all that when it cuts off one end of the PAR, revealing the PAR's built-in ligand.

This ligand loops back to bind to the PAR's receptor, allowing the PAR to activate itself. The activated PAR then provides the cell with instructions to perform certain actions. For example, if the PAR exists inside a fibrinogen cell, it may tell the cell to morph into fibrin. The end result in the thrombin-PAR process is a destructive blood clot that can cause a heart attack, stroke, or other vascular disease.

Since making their initial observation, Coughlin and his team have uncovered four PARs, aptly named PAR1, PAR2, PAR3, and PAR4. While thrombin is responsible for setting off the signaling process in PARs 1, 3, and 4, the team has discovered that the proteases trypsin and tryptase initiate the process for PAR2. Based on this discovery, Coughlin noted, he has "no reason to believe we have identified all of the physiological activators" in what he terms the "coagulation cascade."

Coughlin is currently taking his research to the next level through in vivo mice studies, which is where his second story began. As a result of their studies, Coughlin and his colleagues have discovered that blocking the interaction between thrombin and some PARs may prevent the formation of blood clots. These findings promise to lead the team to a host of additional discoveries about PARs, thrombin, and the formation of blood vessels in general. Coughlin hopes to crystallize their results in ongoing animal research, which, he concluded, leaves his second story open-ended to a vast range of possible advances in vascular disease. ✓