Bleeding Disorder Breakthroughs

Since legendary hematologic researcher Sol Sherry, MD, recruited him to Temple in 1979, **A. Koneti Rao, MD, FACP, FAHA**, has studied bleeding and clotting complications in conjunction with a variety of conditions: diabetes, cardiovascular disease, sickle cell disease, and certain cancers. But his research interest in studying inherited platelet disorders has earned him renown as a pioneer in his own right.

Rao, the Sol Sherry Professor of Medicine and Co-Director of the Sol Sherry Thrombosis Research Center at Temple, has devoted most of his career to uncovering the molecular and genetic mechanisms that predispose individuals to platelet disorders.

Tiny cells that circulate within blood, platelets bind together to form a clot when they detect damage. "Without them, you would bruise excessively and would have prolonged bleeding when you got a cut," explains Rao, who has also served as Associate Dean for Temple's MD/PhD program and as Chief of Hematology.

Rao and his colleagues have been the first to pinpoint several inherited platelet abnormalities. One of their most significant discoveries involved identifying a mutation in a protein called RUNX1 in a child with a bleeding disorder.

"RUNX1 is a transcription factor, a protein that regulates how genes are expressed in cells — so we expected it to regulate a number of genes downstream," Rao says. "To figure out which ones, we used expression profiling, an amazing technology that essentially allows you to look at thousands of genes at once."

The team found 70 downregulated genes in the patient with the RUNX1 mutation and set out to analyze their roles in platelet function — an effort that has revealed numerous connections to platelet defects.

Rao's deep dive into RUNX1 with multiple collaborators has spurred some fortuitous findings. For example, in a study published in 2016 in *EBioMedicine*, they describe a property of aspirin that regulates RUNX1 gene expression, noting that RUNX1 levels might help predict whether patients with cardiovascular disease will have future heart attacks. Aspirin's ability to ward off heart attacks and disease had been established for decades, but scientists never fully grasped how. Rao's work extends this understanding.

Another striking discovery stemmed from an outside study tying increased platelet expression of a gene called PCTP (phosphatidylcholine transfer protein) to faster blood clotting in black individuals versus white individuals.

"When I saw that paper, I said, 'Wow, that was one of the genes that decreased in our RUNX1 patient, and we had no idea what it was.' We dropped everything to see if PCTP was a true target of RUNX1, and the answer was yes," recalls Rao, whose group went on to reveal that PCTP blood levels in patients with chest pain correlated with future heart attacks. The study, done in collaboration with Duke University, was published in *Circulation* last year.

"We started our RUNX1 research with a bleeding disorder and ended up with relevance to heart disease, so we've really covered a full spectrum," says Rao, whose work has been published in dozens of other journals, including *Blood*, the *Journal of Thrombosis and Haemostasis*, and *Platelets* (for which he was founding editor).

Rao, who has had continuous funding from the National Institutes of Health since the 1980s, recently received a new $2.5 million grant to continue studying RUNX1. This time, he is examining endocytosis in platelets — how they pick up and transport various proteins from blood plasma — and whether RUNX1 mutations affect this process. "By understanding basic platelet function through studies of individuals whose platelet function is abnormal, we get information that can be used to develop new medications for disorders where there are blood clots you don't want. Say we find something missing in a patient with a platelet function defect — then a drug that causes that within normal platelets can be developed to treat heart disease by preventing clots," he says.

"This is how science works. You build from one thing to the next, and it has no end," he says.

Photograph by CARDONI

A. Koneti Rao, MD, FACP, FAHA