New Study Reveals Ways to Better Inhibit Blood Clots

Georgia Tech Institute of Technology

Fibrin, the primary ingredient of blood clots, creates a fibrous network that stems the loss of blood at an injury site. But beyond this essential work, fibrin can also cause heart attack, stroke and tissue damage by forming clots that block blood vessels.

Fibrin forms when an enzyme removes parts of a blood protein called fibrinogen, exposing "knobs" that fit into "holes" located on both ends of fibrinogen molecules. Uncovering these knobs allows the fibrinogen molecules to attach to one another, forming a fibrin network. To inhibit unwanted fibrin formation, researchers have developed synthetic knobs to fill the holes, but the best amino acid sequence and structure for these knobs have not been well investigated.

A new study published online in the journal *Blood* reveals factors that could improve the binding of synthetic fibrin knobs to holes and the structures of these knobs in solution. The study also identifies a novel synthetic knob that displays a 10-fold higher affinity for fibrinogen holes than current synthetic knobs. This research was supported by the National Institutes of Health and the Wallace H. Coulter Foundation.

"Understanding the fundamentals of this knob-hole interaction will lead to a more thorough knowledge of fibrin assembly mechanisms and allow us to establish criteria for designing superior anticoagulants with high hole affinity that can inhibit fibrin assembly," said Thomas Barker, an assistant professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

Barker, postdoctoral fellow Sarah Stabenfeldt and School of Computational Engineering graduate student Jared Gossett investigated the interactions between holes and short synthetic peptides modeled after real fibrin knob sequences. They focused specifically on modeling the binding interaction and characterizing the structure of the peptides in solution.

Using a technique called surface plasmon resonance, the research team explored the role of structural and electrostatic properties in regulating the binding of knobs to holes. The structural properties of knob peptides in an aqueous environment had not been examined previously because the small peptides could not be crystallized for structural X-ray studies.

"Researchers previously measured how knob molecules bound to holes in a saturated solution," explained Barker, "but we wanted to know how fast the knobs were binding to the holes and the length of time the knob and hole interacted to

determine if we could optimize these parameters to inhibit fibrin formation."

The researchers measured the hole binding characteristics of six different knob sequences -- each seven or eight amino acids in length -- to evaluate the impact of additional backbone stabilization and/or different charge distributions. They found that the binding rates improved significantly by adding two amino acids, called proline and phenylalanine, for stabilization and having charged configurations in the sixth and seventh positions in the sequences.

"Investigating these binding events under dynamic conditions provided critical information, but the results didnt really surprise us," noted Barker. "Small peptides in aqueous solutions â€˜wiggle a lot, so the more stable the molecules are in their active structural state, the better chance they have of establishing a good knob-hole interaction because theyre not changing their shape as much."

Analyzing the structural dynamics of the peptides through simulation indicated that the orientation of the arginine amino acid side chain and backbone stability contributed significantly to functional binding of the knobs and holes.

During their investigation, the researchers also identified a novel knob peptide mimic (GPRPFPAC) that exhibited a binding rate to holes one order of magnitude higher than previously published knob sequences -- even surpassing the binding activity of the gold standard mimic (GPRPAAC). Future studies will involve modifying this novel peptide further to enhance its ability to inhibit fibrin formation for applications when blood clotting is undesirable.

The surface plasmon resonance and modeling techniques used in this study enable peptide sequences to be modified and optimized to control the typical wound healing matrix.

"An additional goal for this technology is to develop a viable delivery strategy for synthetically engineered fibrin glue so that we can guide and control the bodys response to an injury," added Barker.

Shuming Nie, the Wallace H. Coulter Distinguished Faculty Chair in Biomedical Engineering, and Steve Harvey, a professor in Georgia Techs School of Biology, also contributed to this research.

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