Medical Xpress

Jamming the signal

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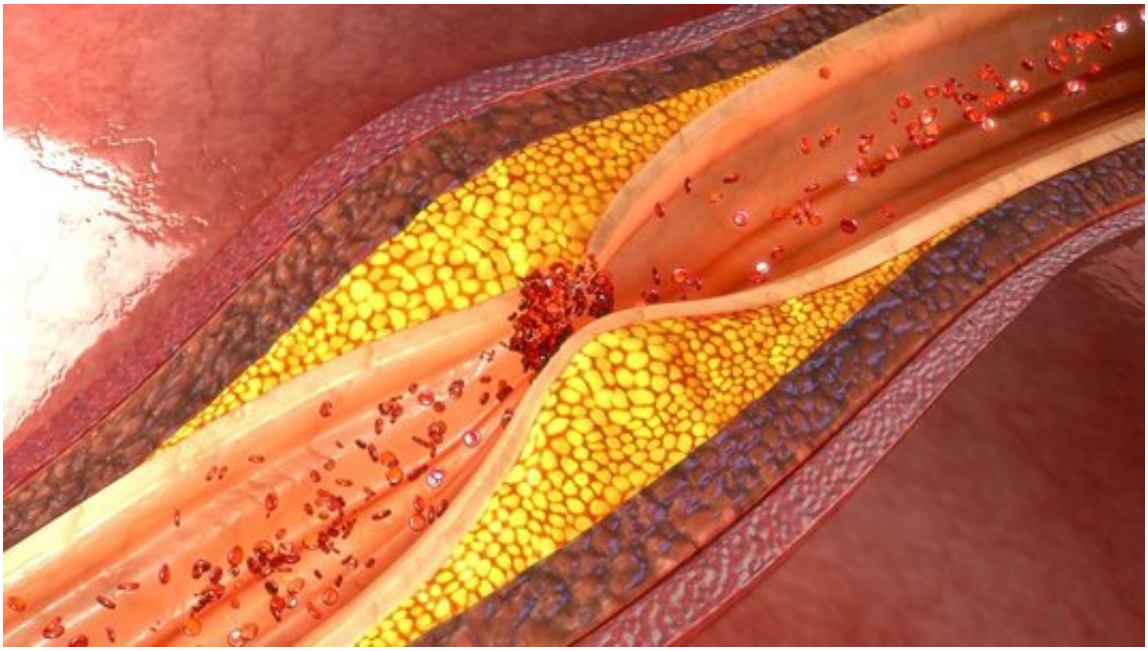

Coronary artery plaque rupture and thrombus formation. Credit: 7activestudio/fotolia.com

The formation of blood clots in atherosclerotic arteries results in myocardial infarction and stroke. New research at LMU now demonstrates that low doses of agents developed to treat leukemia can selectively inhibit atherosclerotic plaque-induced thrombus formation.

The rupture or erosion of atherosclerotic deposits (plaques) piling up in the inner layer of arteries exposes material to the blood stream that stimulates the adhesion and aggregation of blood platelets (and the

subsequent formation of thrombi) which can precipitate heart attacks and ischemic strokes. Several proteins play key roles in this complex process, including receptors on the platelet surface that bind to plaque collagens. Professor Wolfgang Siess and his colleagues at LMU's Institute for the Prophylaxis and Epidemiology of Cardiovascular Diseases have now shown that drugs which are used for the treatment of certain forms of leukemia specifically inhibit the formation of atherosclerotic plaque-triggered thrombus formation – and they do so more effectively than the agents currently employed for this purpose. Their findings appear in the journal *Blood*.

Two receptors found on platelet, glycoproteins Ib and VI, are critically involved in initiating the formation of plaque-induced thrombi. Earlier work had shown that antibodies against these receptors reduce thrombus formation triggered by atherosclerotic plaques more effectively than do standard anti-platelet therapies. "Since signal transmission by these receptors is essential for platelet activation by plaques, we suspected that inhibition of the signal pathway downstream of these receptors should also effectively suppress thrombus formation," Siess explains. The LMU researchers have now confirmed this hypothesis by inhibiting an enzyme known as Bruton's tyrosine kinase (Btk). When glycoprotein Ib or VI bind to their respective ligands, Btk gets activated and triggers a signal cascade that activates platelets. Oral intake of pharmacological inhibitors of Btk, such as ibrutinib, irreversibly blocks this process. Ibrutinib is already in clinical use for the treatment of chronic lymphocytic leukemia , and recently an even more selective Btk inhibitor (acalabrutinib) has been approved by the FDA to combat other B-cell malignancies.

The new study demonstrates that ibrutinib and two of the newer Btk inhibitors (acalabrutinib and ONO/GS-4059) specifically prevent the aggregation of platelets induced by their interaction with atherosclerotic plaques – both under static conditions and in the presence of shear forces like those associated with arterial blood flow. Of note, inhibition

of Btk had no effect on normal thrombus formation, in which platelet aggregation is stimulated in flowing blood by interaction with the collagens found in normal connective tissues. Importantly, in healthy subjects, very low doses of ibrutinib were sufficient to block plaque-induced platelet aggregation. This is attributable to the irreversible nature of its inhibitory effect on Btk and to the fact that platelets lack nuclei and cannot synthesize new copies of the Btk protein to replace the inactivated molecules. Given the very low dose required, it should be possible to selectively inhibit Btk in platelets without compromising the functions of other cell types in which the enzyme is expressed. "As orally bioavailable Btk inhibitors selectively and more potently inhibit plaque-induced thrombus formation than the drugs now employed, we assume that they will prove to be more suitable for the prophylaxis and therapy of myocardial infarction and ischemic stroke," says Siess. "This is a first, encouraging step towards the application of Btk inhibitors for the prevention and therapy of these cardiovascular diseases."

More information: Kristina Busygina et al. Oral Bruton tyrosine kinase inhibitors selectively block atherosclerotic plaque-triggered thrombus formation, *Blood* (2018). DOI: 10.1182/blood-2017-09-808808

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