A 'switch' that regulates traffic across blood vessels

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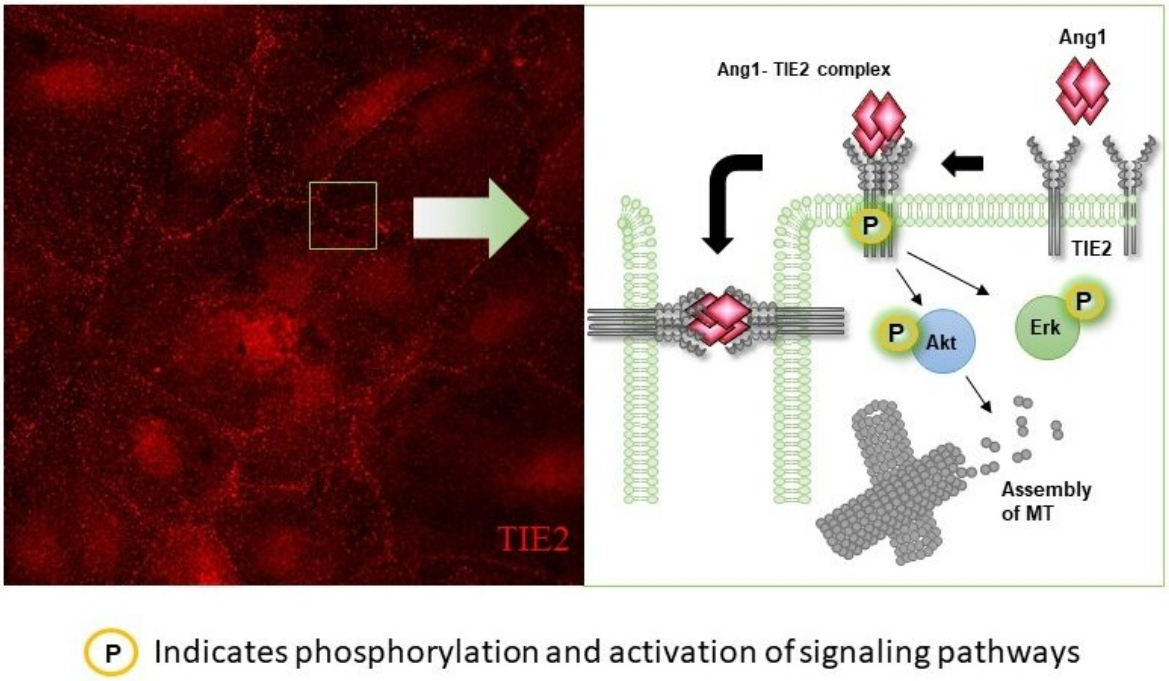

Proposed mechanism of Angiopoeitin-1 (Ang-1) induced anti-permeability effect in human microvascular endothelial cells. The image on the left shows blood vessels cells that are stained to identify the location of the protein TIE2. When the activator Angiopoeitin-1 (Ang-1) is applied, TIE2 are localised near the cell surface where Ang1-Tie2 forms a bridge that holds cells together. In subsequent experiments, it is demonstrated that Ang1 binding could mediate cellular changes through increasing either phosphorylation of Akt or Erk which then helps to stabilise the microtubules to maintain cellular structure. Credit: National University of Singapore

NUS scientists have discovered a control mechanism that regulates the traffic of cells and substances across blood vessels. This effect can have significant impact on cancer metastasis.

Nanoparticles are being used in various biomedical applications, including the diagnosis and treatment of cancer. Drug releasing nanoparticles could be programmed to deliver drugs locally at the tumour site. However, recent studies have shown that these nanoparticles can lead to the formation of micrometre-sized gaps in the walls of blood vessels, making them "leaky." In cancer patients, these gaps could make it easier for surviving cancer cells to escape from their primary sites into other parts of the body.

A research team comprising Prof HO Han Kiat from the Department of Pharmacy, NUS and Prof David LEONG from the Department of Chemical and Biomolecular Engineering, NUS discovered that Angiopoeitin-1 (a type of protein) can help to close the gaps in the blood vessels caused by nanoparticles and reduce their permeability. This, in turn, controls the passage of substances and molecules through the walls of the blood vessels. By adjusting the amount of Angiopoeitin-1 in the body, the researchers found that they can limit and reverse the "leakiness" induced in blood vessels caused by nanoparticles in biomedical applications.

In their experiments, the research team administered breast cancer cells beneath the skin of murine models and then introduced titanium dioxide nanoparticles into their blood vessels. They established that the nanoparticles increased the leakage of cancer cells into the blood vessels. This leakage effect can enhance the movement of circulating cancer cells to distant tissues, which may result in the formation of new secondary cancer sites previously not accessible to the cancer cells.

Following up on this, the team found that Angiopoeitin-1 acts as a

growth factor to TIE2, a cell surface regulator found naturally in our blood vessels. When there are more Angiopoeitin-1, TIE2 protein is localised and stimulated to close up the gaps in the blood vessels which could be caused by the nanoparticles. This in turn reduces the permeability of the blood vessels and limits the amount of cancer cells leaking into the blood stream.

Prof Ho said, "The study showed that Angiopoeitin-1 could potentially be used as a counter mechanism to limit and reverse the leakiness induced by nanoparticles. This helps to decrease the extravasation and transportation of cancer cells to other tissues in cancer patients."

More information: Jie Kai Tee et al. Angiopoietin-1 accelerates restoration of endothelial cell barrier integrity from nanoparticle-induced leakiness, *Nanotoxicology* (2019). DOI: 10.1080/17435390.2019.1571646

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