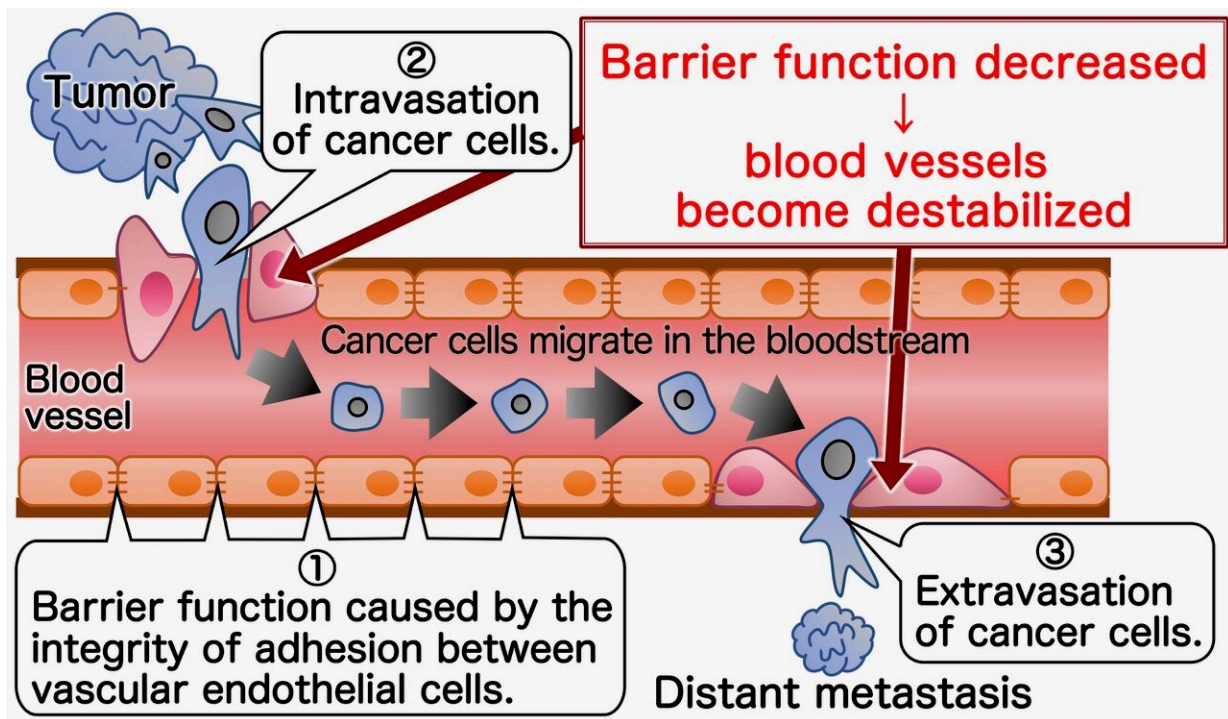


Promotion of cancer progression via extracellular vesicles

November 10 2022



Usually, blood vessels are stabilized, and their barrier function is maintained by the tight adhesion between vascular endothelial cells (①). When cancer cells metastasize to distant organs via blood vessels, the morphology of vascular endothelial cells changes in response to the growth factors or cytokines secreted by the cancer cells. This results in the loss of adhesion between vascular endothelial, destabilization of the vessels and loss of their barrier function. These changes facilitate invasion, "intravasation" (②) of cancer cells into blood vessels and allow the cancer cells to travel through the body in the bloodstream. When cancer cells reach the distant organs, they migrate out of the blood vessels in a process called "extravasation" (③) by inducing vascular destabilization, followed

by formation of distant metastatic sites. Credit: Department of Biochemistry, TMDU

The advent of cell phones, the internet, and various messaging platforms has allowed for faster and broader communication worldwide. But did you know that your body has its own complex communication system in the form of extracellular vesicles (EVs)?

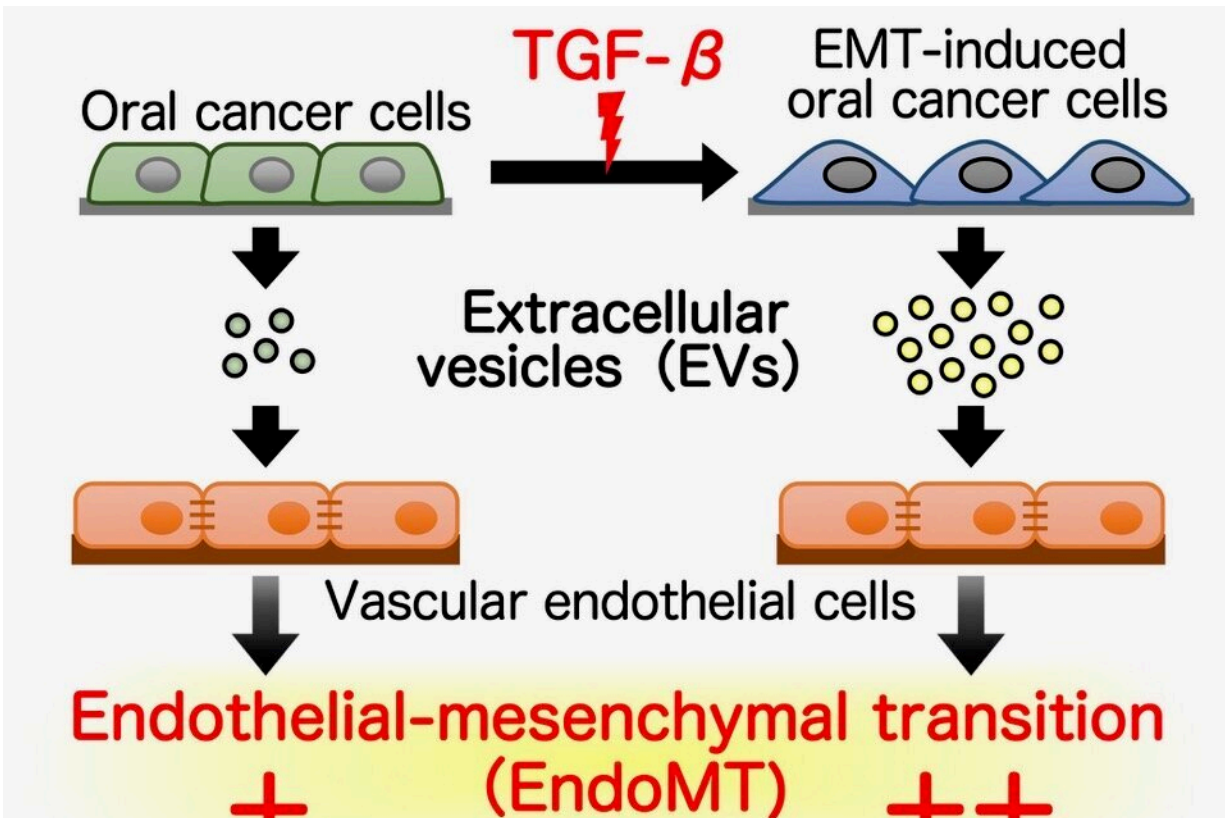
These small structures, which contain cellular "cargo" such as protein and [nucleic acids](#), are secreted by cells and can travel throughout the body, influencing a variety of physiological and pathological processes. Recently, researchers in Japan have shed new light on the role of EVs in the progression of cancer.

In a new study published in *Inflammation and Regeneration*, researchers led by Tokyo Medical and Dental University (TMDU) examined the effects of oral cancer cell-derived EVs in endothelial-mesenchymal transition (EndoMT). EndoMT is a process in which endothelial cells, or cells that line the [blood vessels](#), lose their characteristics and take on properties of mesenchymal cells.

While EndoMT occurs normally during [embryonic development](#), it has also been shown to destabilize vascular structures such as blood vessels. In cancer, vascular destabilization may make it easier for cancer cells to enter and exit the bloodstream, thereby promoting metastasis.

Previous research has shown that cancer cells release EVs that act to induce a similar process called [epithelial-mesenchymal transition](#) (EMT), thereby promoting tumor development. However, the effects of cancer cell EVs on EndoMT in normal vascular endothelial cells have not yet been elucidated. Therefore, the TMDU-led research team set out to

characterize EVs released by oral cancer cells and to investigate the effects of these EVs on healthy vascular endothelial cells.



In exacerbated oral cancer cells via TGF- β -stimulated epithelial-mesenchymal transition (EMT), the amount of secreted EVs increased as compared to unstimulated oral cancer cells. TGF- β -stimulated oral cancer cell-derived EVs induced endothelial mesenchymal transition (EndoMT) in normal vascular endothelial cells to higher extent if compared with effect induced by EVs from non-stimulated oral cancer cells. In addition, the treatment of vascular endothelial sheets formed by endothelial cells with these EVs induced the formation of gaps in vascular endothelial sheet leading to increased permeability. Our results suggest that TGF- β -stimulated EMT-induced oral cancer cells contribute to cancer metastasis by secreting EVs that induce EndoMT in vascular endothelial cells and enhance vascular destabilization. Credit: Department of Biochemistry, TMDU

"A signaling factor known as transforming growth factor- β (TGF- β) has been shown to induce EMT in cancer cells, so we began by investigating characterized changes of human oral cancer cells brought by TGF- β -induced EMT," says lead author Miho Kobayashi. "We found that oral cancer cells exposed to TGF- β released roughly three times as many EVs as those that were not exposed."

The research team next incubated human vascular [endothelial cells](#) with EVs from TGF- β -exposed cells or EVs from cells that were not exposed to TGF- β . RNA and protein analysis showed increased expression of mesenchymal cell markers and decreased expression of endothelial cell markers in vascular cells exposed to EVs secreted from cancer cells that were exposed to TGF- β .

"The changes in endothelial and mesenchymal marker expression in the vascular [cells](#) indicated that EndoMT was induced by EVs from oral [cancer cells](#) in which EMT had occurred," says lead author Kashio Fujiwara. Furthermore, evaluation of the effects of cancer cell-derived EVs on vascular stability in human vascular endothelial monolayer cultures showed that treatment with the EVs enhanced vascular destabilization.

This research provides further understanding of the mechanisms involved in EndoMT and vascular instability, which may aid in the development of therapeutic treatments to disrupt [cancer](#) progression and metastasis.

More information: Miho Kobayashi et al, Transforming growth factor- β -induced secretion of extracellular vesicles from oral cancer cells evokes endothelial barrier instability via endothelial-mesenchymal transition, *Inflammation and Regeneration* (2022). [DOI: 10.1186/s41232-022-00225-7](https://doi.org/10.1186/s41232-022-00225-7)

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