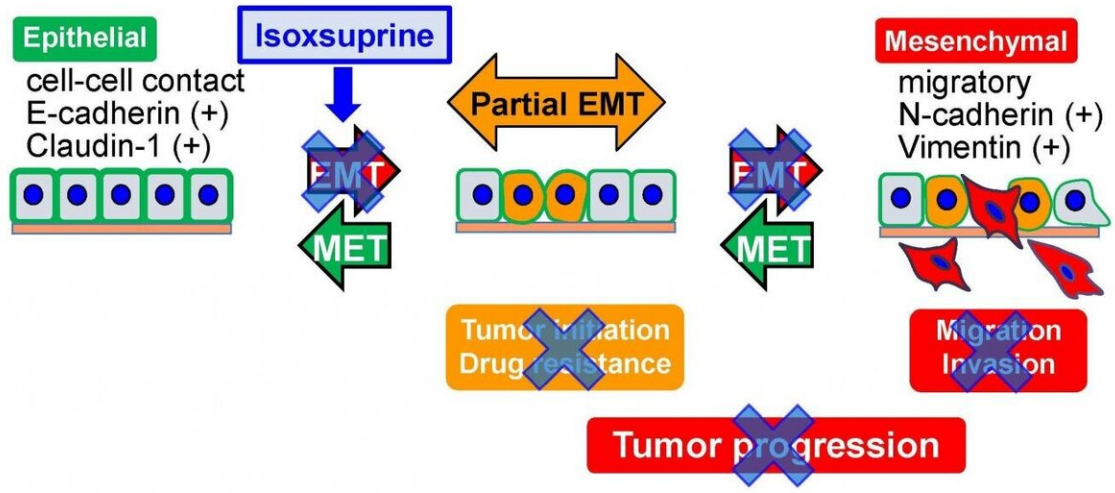
Beta2-AR agonist therapy puts the brakes on oral cancer progression

December 4 2020



In this study we identified isoxsuprine, a β2-adrenergic receptor agonist as an effective inhibitor of mesenchymal phenotypes and migration of oral squamous cell carcinoma cells suggesting that β2-adrenergic receptor signal is a new promising therapeutic target for treatment of oral cancer. Credit: Department of Biochemistry,TMDU

Affecting almost 600,000 people worldwide every year, and with only a 50% survival rate, oral squamous cell carcinoma (OSCC) is one of the more common and deadly forms of cancer. The poor prognosis of OSCC patients is mainly attributed to a lack of therapies that block the

metastasis, or spread, of cancer cells from the primary tumor to other sites in the body.

Prior to metastasis, cancer cells undergo a series of changes that cause them to become motile and more invasive. This process, called epithelial-mesenchymal transition (EMT), equips cancer cells with everything they need to travel through the lymphatic system and form secondary tumors. Furthermore, recent reports imply that EMT also confers cancer cells with tumor initiation activity and drug resistance.

Working on the theory that disrupting EMT should prevent cancer progression and therefore reduce OSCC mortality rates, researchers from Tokyo Medical and Dental University (TMDU) screened a panel of small chemical compounds for their ability to reverse the process of EMT in oral cancer cells. The results, published this month in *Cancer Science,* may represent an exciting new avenue for the treatment of OSCC.

"We identified a beta2-adrenergic receptor (β2-AR) agonist called isoxsuprine that effectively interfered with EMT," says lead author of the study Shintaro Sakakitani. "Interestingly, previous studies have provided conflicting results regarding the involvement of β-ARs in tumorigenesis—some reports suggest that β-AR signaling is important in tumor progression, while others point to a protective role for β-AR induction."

After treating a range of oral cancer cell types with isoxsuprine, the researchers found that the resulting increase in β2-AR expression significantly impaired EMT and reduced cell motility. A non-selective agonist called isoprenaline, which enhances the expression of all types of β adrenergic receptor not just β2, produced a similar result.

Confirming the protective role of β-AR activation, the researchers then

pre-treated cells with a chemical that prevents receptor expression, resulting in enhanced EMT. Further, deletion of the gene coding for β2-AR completely abolished the protective effects of isoxsuprine.

As a further test of treatment efficacy, the researchers established tumors in mice and provided daily treatment with either isoxsuprine or a placebo. Not surprisingly, at the end of the treatment period, mice that received isoxsuprine had significantly smaller tumors compared with the placebo group, confirming the tumor-suppressive effects of isoxsuprine.

"These results are hugely encouraging," says senior author Katarzyna Anna Podyma-Inoue. "The efficacy of β-AR-agonist therapy in both the in vitro and in vivo models suggests that this group of compounds may be the answer to preventing metastasis in OSCC and could potentially even inhibit tumor growth, offering a much better prognosis for OSCC patients worldwide."

More information: Shintaro Sakakitani et al, Activation of β2-adrenergic receptor signals suppresses mesenchymal phenotypes of oral squamous cell carcinoma cells, *Cancer Science* (2020). DOI: 10.1111/cas.14670

Provided by Tokyo Medical and Dental University