How head and neck squamous cell carcinomas take over wound-healing processes

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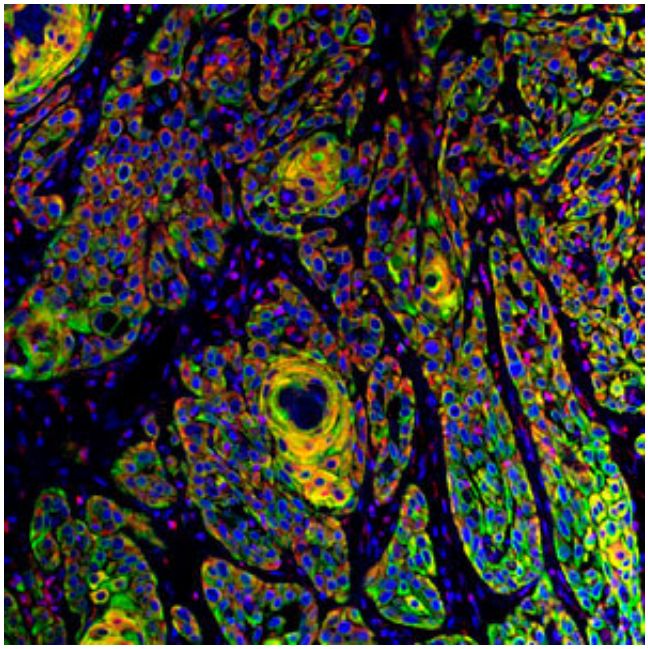

Elevated expression of DIAPH1 protein (shown in red) in a squamous cell carcinoma patient. Credit: A*STAR Institute of Medical Biology

A*STAR researchers have identified the molecular means by which a common form of cancer hijacks wound-healing processes to help it spread. The team hope their findings could lead to more effective treatments.

Head and neck squamous cell carcinoma (HNSCC) is the sixth most frequently-occurring cancer worldwide. It is caused by the uncontrolled growth of squamous cells—thin, flat, scale-like cells—in the outer layer of skin called the epidermis.

Upon injury, epidermal cells called keratinocytes proliferate and migrate toward wounds, a process that normally stops when healing is complete. In 2013, Prabha Sampath's group at the A*STAR Institute of Medical Biology discovered a molecular switch that triggers the production of a microRNA called miR-198 in healthy skin, and, upon injury, of the protein follistatin-like 1 (FSTL-1).

Given that uncontrolled cell growth and migration are hallmarks of cancer and a primary cause for metastasis, Sampath's team set out to test their hypothesis that a defective wound-healing switch could facilitate HNSCC.

They used a technique called fluorescent in situ hybridization to show that miR-198 was expressed in abundance in tongue cells from healthy patients, but absent from those from HNSCC patients. Their finding of elevated FSTL1 expression in HNSCC samples suggested the molecular switch was indeed defective. In the absence of miR-198, they also found increased expression of Diaphanous-1 (DIAPH1), another protein elevated following skin wounding.

Using biochemical and cell culture experiments, the researchers went on to show that a protein that triggers cell growth and differentiation called epithelial growth factor (EGF), which is often elevated in HNSCC, acts as a regulator of the defective switch. They revealed the precise molecular mechanism involved.

Sampath's group further showed that blocking FSTL1 and DIAPH1 individually not only thwarts the ability of HNSCC cancer cells to migrate, but also limits the spread of metastatic tumors in immunodeficient mice. Notably, knocking out both genes simultaneously prevented formation of metastatic tumor nodules. Analysis of The Cancer Genome Atlas (TCGA) data base showed the survival of HNSCC patients who expressed elevated levels of both FSTL1 and DIAPH1 was significantly shorter than those who expressed

them at lower levels.

Further investigation revealed FSTL1 and DIAPH1 promote HNSCC metastasis by blocking the actions of other proteins that normally prevent cell migration.

The findings provide new targets for therapeutic intervention. "Additionally, we are trying to identify biochemical modulators of this defective molecular switch which could serve as novel and alternative drugs to effectively treat this deadly disease," says Sampath.

More information: Gopinath M. Sundaram et al. EGF hijacks miR-198/FSTL1 wound-healing switch and steers a two-pronged pathway toward metastasis, *The Journal of Experimental Medicine* (2017). DOI: 10.1084/jem.20170354

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