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A better understanding of how genetics influences responses to mouth cancer drugs could lead to improved treatment

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A single letter DNA mutation is a big determinant of whether patients with advanced oral cancer respond to treatments. Researchers from the National Cancer Centre Singapore (NCCS) and A*STAR who uncovered the mechanisms behind this effect hope their findings will help doctors target treatment more effectively.

Oral squamous cell carcinoma (OSCC) is characterized by the uncontrolled growth of thin, scale-like squamous cells in the outer layer of the mouth. Only around 50 per cent of patients who are treated through surgery or radiotherapy are cured, and the average duration of survival of those with advanced OSCC that recurs following treatment is just 6 to 9 months.

Epidermal growth factor receptors (EGFRs) play important roles in driving the progression of some OSCCs. Drugs that target them, however, only work in a small number of patients.

A 2012 clinical trial led by Daniel Tan at NCCS and A*STAR's Genome Institute of Singapore had found that the EGFR-blocking drug gefitinib worked well in two patients with two copies of the EGFR coding gene with an adenine (A) nucleobase in place of the more common guanine (G) at a particular location.

More recently, tests by Gopal Iyer, also at NCCS, and Tan showed that

OSCC patient-derived cells with the above A/A genotype were sensitive to gefitinib and erlotinib, another EGFR blocker. Those with the G/G or G/A variants exhibited resistance to the drugs.

Editing the DNA of the G/G genotype cells to become G/A at the same location increased their sensitivity to the drugs 70-fold. "We were pretty surprised it had such a dramatic effect," says Iyer.

The genetic mutation occurs in a section of DNA that modulates the stability of a long non-coding RNA (lncRNA) known as EGFR-AS1. Gene expression tests showed that levels of this lncRNA were significantly higher in G/G genotype cells than in A/A cells.

When cells with the G/G genotype were exposed to small interfering RNAs that reduced their production of EGFR-AS1, their sensitivity to EGFR-blocking drugs increased significantly.

They also found that the tumors of seven patients with the A/A genotype shrank following treatment with EGFR-inhibiting drugs.

While the mechanism underlying this effect is not fully understood, the group has demonstrated that cells of the G/A and A/A genotypes produced higher ratios of one of four variants of EGFR relative to another, and that EFGR-AS1 helps mediate this difference.

Iyer said that new RNA-interference therapies could be developed to target cancers dependent on EGFR signaling. The group is conducting a larger human trial to better understand the biomarkers that could provide for improved targeting of existing treatments.

More information: Daniel S W Tan et al. Long noncoding RNA EGFR-AS1 mediates epidermal growth factor receptor addiction and modulates treatment response in squamous cell carcinoma, *Nature*

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