

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

Iver 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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