The paradoxical roles of well-known cancer genes are mediated by oxygen levels in breast cancer

January 4 2017

Oxygen deprivation, or hypoxia, has been identified by A*STAR researchers as a key factor in switching the function of major cancer genes from tumor-promoting to tumor-suppressing in a breast cancer subtype, suggesting the need for differential therapies in cancer treatments.

A number of key genes are associated with promoting or suppressing tumor formation and/or migration and invasion in several human cancers. Polycomb repressive complex 2 (PRC2) and enhancer of zeste 2 (EZH2) are two genes that appear to be significant in both promoting and suppressing tumor formation. A team led by Qiang Yu from the Genome Institute of Singapore at A*STAR were surprised to find that hypoxia was the key factor for promoting EZH2-mediated tumor invasion and, therefore, for poor clinical outcome in triple-negative breast cancer (TNBC).

These findings may have significant consequences for developing future therapies. "Different cancers are driven by different mechanisms and some signaling components, such as the EZH2/PRC2 complex, can be both tumor-suppressive and tumor-promoting," says Yu, "and therefore context dependency is always an important factor when it comes to targeted therapies."

Yu and his team discovered this paradox by examining the chemical

pathways of these genes in breast cancer cells. They showed that hypoxia leads to impaired PRC2 expression but promotes EZH2 partnering with another tumor-promoting gene, FoxM1. Together EZH2 and FoxM1 increase expression of the cancer migration promoting gene, matrix metalloproteinase (MMP), and enhance tumor migration.

"The double face of EZH2 as both a tumor suppressor and an oncogene, and hypoxia to facilitate a switch of the dual functions were surprising," explains Yu. "This helped to explain how hypoxia can promote growth and invasion."

Examining these factors in breast cancer was important because PRC2 and EZH2 appeared to be expressed at differential levels in breast cancer subtypes, suggesting that they may not always function together. In particular, they have opposite expression levels—PRC2 is low and EZH2 is high—in the TNBC subtype, which is highly aggressive and kills more patients than any other breast cancer. Therefore, the switching of partners by EZH2 from PRC2 to FoxM1 may be responsible for mortality.

This mechanism may also explain the apparently paradoxical nature of EZH2 in other cancer types. "This may be also seen in other instances, as non-canonical EZH2 activity has also been documented in other cancers," notes Yu.

More information: Sylvia Mahara et al. HIFI-α activation underlies a functional switch in the paradoxical role of Ezh2/PRC2 in breast cancer, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1602079113

Provided by Agency for Science, Technology and Research (A*STAR),

Singapore