Two cancer-causing genes work together to promote metastasis

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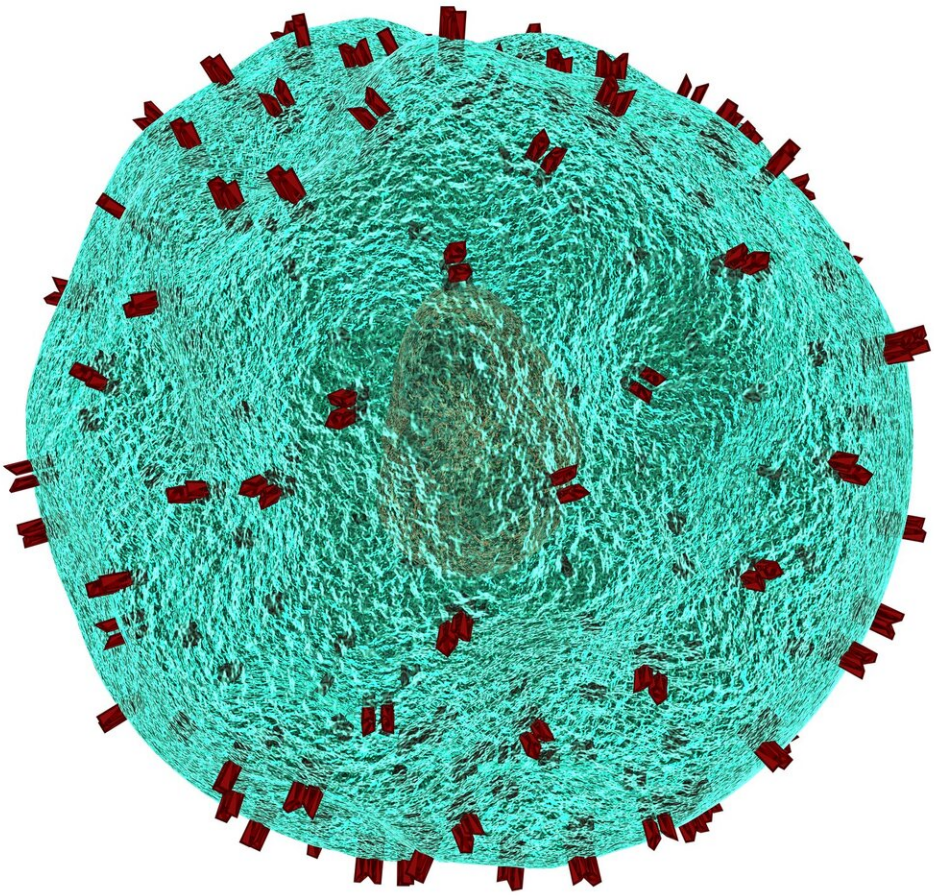

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Cancer-promoting genes MYC and TWIST1 co-opt immune system cells to enable cancer cells to spread, but blocking a key step in this process can help prevent the disease from developing.

These findings, published today in *eLife*, may help clinicians to identify cancer patients at risk of metastasis, a process where cancer cells spread to other parts of the body. They may also inform the development of new strategies to prevent or treat metastasis.

"Most cancer-related deaths are caused by metastasis, but there are currently no treatments available to stop it," explains lead author Renumathy Dhanasekaran, a Ph.D. student in the Division of Gastroenterology and Hepatology at Stanford University, California, US. "The main goal of our research is to understand how cancer-causing genes enable metastasis and use that information to identify targeted therapies that may prevent it."

Dhanasekaran and her colleagues genetically engineered mice to express both MYC and TWIST1 and found that these two major cancer-promoting genes led to metastases. They also saw that the cancer cells produced inflammation-promoting molecules Ccl2 and Il13, which attract immune cells called macrophages and make them more tumour-cell friendly. This makes it easier for the cancer cells to migrate to new areas of the body.

The team next showed that exposing mice with liver cancer caused by MYC alone to Ccl2 and Il13 causes metastasis. But blocking this specific combination of cytokines appeared to hinder the process.

To see if the two genes also contributed to metastases in humans, the scientists analysed 10,000 samples of tumours collected from humans with 33 different types of cancer. They found that patients with MYC and TWIST1 were less likely to survive, produced more Ccl2 and Il13, and had more macrophages in their tumours.

"Interestingly, MYC and TWIST1 have previously been shown to cooperate in a positive way to modulate inflammation during embryonic development," says senior author Dean Felsher, Ph.D., Professor in the Division of Oncology at Stanford University. "These microenvironment changes are needed to enable mesodermal cells to migrate to their destination. But in multiple human cancers, both MYC and TWIST1 are over-expressed, and we suggest that they in turn cause tumour invasion by 'hijacking' this embryonic cell migration program."

Finally, the team monitored Ccl2 and Il13 levels in 25 patients with liver cancer and 10 control patients with cirrhosis. They found that only the patients with liver cancer had elevated levels of the two molecules and, of this group, those with higher levels of Il13 were more likely to have aggressive tumours.

"These results suggest that patients with more aggressive cancers will likely have higher levels of Ccl2 and Il13 cytokines in their blood," Felsher concludes. "Testing for these molecules in future could help identify those who may benefit from combination therapies that target them."

More information: Renumathy Dhanasekaran et al, MYC and Twist1 cooperate to drive metastasis by eliciting crosstalk between cancer and innate immunity, *eLife* (2020). DOI: 10.7554/eLife.50731

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