Scientists uncover a startling and exploitable coordination of gene expression in tumors

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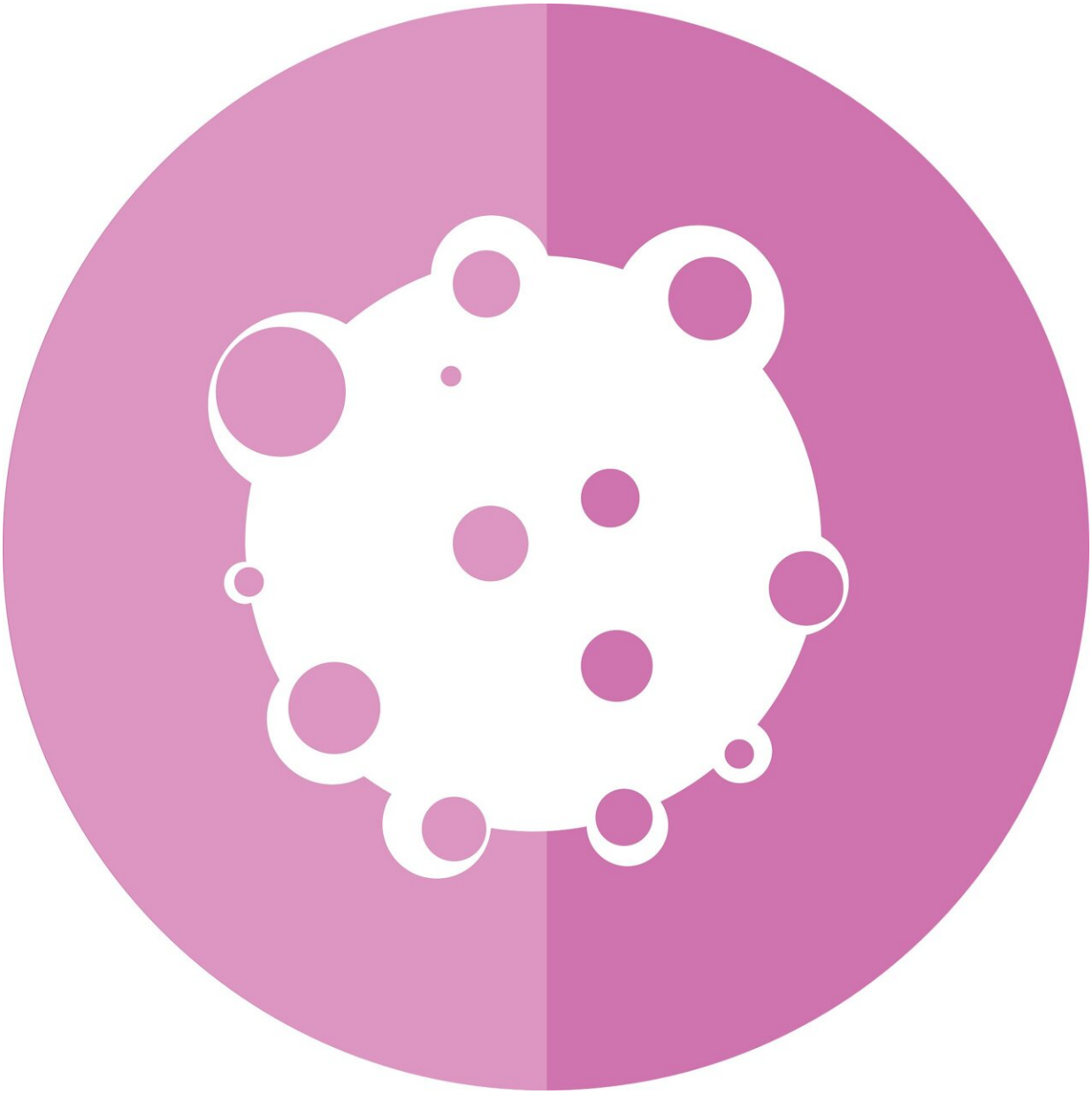

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A Ludwig Cancer Research study has identified a pair of genes whose expression by a type of immune cell within tumors is predictive of outcomes for cancer patients and is linked to a vast network of gene expression programs, engaged by multiple cell types in the tumor microenvironment, that control human cancers.

Researchers led by Ludwig Lausanne's Mikaël Pittet report in the current issue of *Science* that patients with higher expression of the gene CXCL9 in their tumor-associated macrophages had far better clinical outcomes than those with higher expression of a gene named SPP1 by the immune cells. Macrophages expressing the former gene, they show, are invariably poised to attack cancer cells, while those expressing SPP1 are in a state supportive of tumor growth. Most intriguing, however, is the discovery that when the ratio of CXCL9 to SPP1 is high in the tumor microenvironment (TME), gene expression programs in other TME cells indicate a similarly anti-tumor slant; a low CS ratio, on the other hand, invariably accompanies pro-tumor gene expression signatures across the TME.

"We were very surprised to find that just this one parameter—the ratio of two genes primarily expressed by macrophages—could tell us so much else about the tumor," said Pittet. "This is true for multiple types of solid tumors. It means that despite their enormous complexity, the microenvironments of tumors are governed by a clear set of rules. We have described one of them in this study."

With further validation in prospective clinical studies, Pittet noted, the CS ratio could be an easily measured molecular marker of likely patient prognosis and a useful tool for the management of therapy. Beyond that,

the networks of linked gene expression signatures across cell types identified by the study expose several potential molecular targets for the development of drugs that might tip the TME into a state more susceptible to treatments like immunotherapy.

Noncancerous cells of the TME play a critical role in the growth and viability of tumors. These include fibroblasts, which churn out the molecular filler of tissues, endothelial cells that build blood vessels, epithelial cells that line body cavities and a menagerie of immune cell species that variously help or hinder tumor growth. The possibility of targeting these cells to treat cancers is tantalizing, because unlike malignant cells, they do not mutate rapidly and are thus unlikely to evolve resistance to therapies.

Pittet and his colleagues were interested in how much the TME varies between tumors. To find out, they conducted an unbiased analysis of 52 primary and metastatic tumors from 51 patients with head and neck cancers, examining how global gene expression captured in individual cells but statistically analyzed across tumors as a whole corresponded to patient outcomes.

This approach identified CXCL9 and SPP1—whose expression is mutually exclusive in individual macrophages—as being tightly linked to prognosis, and this turned out to be true for other solid cancers as well. The expression of the two genes, Pittet and colleagues show, is also more categorically associated with the anti-tumor or pro-tumor "polarity" of macrophages than currently used markers.

Notably, the ratio of CXCL9 and SPP1 expression (termed CS^{hi} or CS^{low}) was broadly consistent with the state of other types of TME cells in head and neck tumors and with several phenomena associated with pro- and anti-tumor effects. CS^{hi} tumors, for example, tended to be infiltrated with B and T lymphocytes and dendritic cells, which all drive

anti-tumor immunity. Further, other cell types in these tumors engaged signaling molecules and pathways that fuel inflammation or otherwise instigate immune responses.

CS^{low} tumors, meanwhile, bore gene expression signatures associated with cancer growth and progression, such as adaptations to oxygen starvation, the formation of new blood vessels and the induction of cellular transformations that propel cancer metastasis.

"Just by looking at the ratio of these two genes in macrophages, you can deduce the molecular activity of tumor cells, endothelial cells, fibroblasts—you name it," said Pittet. "This startling coherence means that tumors are not a chaotic place, that all these cell states within the TME are coordinated. This information has the potential to be very useful for the development of precision medicine strategies for cancer therapy."

Pittet and his colleagues will next examine whether the gene expression networks identified in their study can be used to prospectively predict patient outcomes or gauge likely responses to various therapies. They will also be looking in more detail at other coordinated axes of gene expression in the TME, how they interact with the CS ratio and how each influences the other.

"The big question is, what are the best ways to interfere therapeutically with this network, with the goal being benefit to the patient?" said Pittet.

More information: Ruben Bill et al, CXCL9:SPP1 macrophage polarity identifies a network of cellular programs that control human cancers, *Science* (2023). DOI: 10.1126/science.ade2292