Researchers uncover an inter-reliance of stromal cells in cancer progression

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Stromal cells are the healthy cells which get drawn into cancer and can facilitate progression of the disease. In this current study, a team of researchers from the School of Cancer & Pharmaceutical Sciences, led

by Dr. James Arnold, uncover an inter-reliance of a subset of macrophages and fibroblasts, in cancer.

Despite the many pro-tumoral processes that have been associated to individual cell types within the stroma, there is less known about the inter-reliance of these cells. There is also a lack of knowledge about the cell types which are responsible for orchestrating the reactions that underpin cancer progression.

Dr. James Arnold, senior author says that "we believe that the concept of identifying the key stromal cell types in orchestrating stromal reactions, and their messenger axes for directing these tasks, could provide novel strategies to target cancer. It is becoming apparent that stromal cells are not working as islands but in collaboration with one another."

In this research, the team characterize a new 'pro-angiogenic niche' involving subsets of macrophages and fibroblasts which sit close to the blood vessel wall within the tumor. They demonstrate that the macrophages residing in this location—characterized using single cell RNA sequencing and in situ labeling techniques—play a fundamental role in orchestrating a pro-angiogenic fibroblast subset to expand and divide with the growing tumor which supports cancer progression.

Dr. James Opzoomer, lead author, says that "this promising work identifies important non-cancerous tumor resident cell types that communicate with each other to support tumor growth. Through better understanding how these stromal cells communicate in the tumor microenvironment, we can develop strategies to disrupt this tumor supporting communication network. We hope that this study will inform the development of the next generation of tumor stroma targeting therapies."

Through a collaboration with the University of Birmingham, the team

were able to use in vivo photo labeling techniques to show that fibroblasts in the tumor are not recruited but rely solely on local proliferation to keep up their prevalence with the growing tumor mass. They showed that macrophages are pivotal to supporting this expansion.

This study, published in *Science Advances*, highlights the inter-reliance of macrophage and fibroblast sub-populations in cancer and could provide novel approaches for therapeutic intervention in cancer, where targeting the key stromal populations/subsets that are playing an orchestrating role could have collateral benefits in indirectly affecting other stromal cells that are reliant on it. To summarize, this could dismantle the stromal network upon which cancers rely.

"There are many benefits for therapeutically targeting the tumor stroma rather than the tumor cells directly, as healthy cells will obey biological rules and, as such, tend to be less prone to adapting resistance mechanisms to therapies," Arnold concludes.

The next step for this research is to understand how to most effectively therapeutically target this pro-angiogenic niche with a view to translation.

More information: James W. Opzoomer et al, Macrophages orchestrate the expansion of a proangiogenic perivascular niche during cancer progression, *Science Advances* (2021). DOI: 10.1126/sciadv.abg9518

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