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Charting the immune landscape in brain cancers

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The brain is one of the most complex organs of the human body. For a long time, it was thought that the brain is hermetically sheltered from entry by invaders, including our body's white blood cells (or "immune cells"). The discovery that different brain cancers contain quite distinct landscapes of immune cells may help us better understand their development and devise novel and effective therapeutic strategies.

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Thanks to revolutionary advances in cancer research, several cancer types can today be treated and controlled over long periods, similar to other chronic diseases. Among the most recent developments are immunotherapies, which aim to activate the patients' immune system to fight cancer. While immunotherapies have radically improved the treatment of a select group of previously devastating cancers, they still are unsuccessful in most brain cancer patients. This is partly because we still know comparatively little about the complexity of brain cancers compared to other cancers, particularly about the role of immune cells.

Therefore we set out to quantify the abundance of immune cells in different brain cancers. In other words: we charted a comprehensive map of the immune landscape of brain cancers to understand better which players are present in this complex environment. We performed this quantification in a large group of 100 patients who donated a piece of tissue from their surgically resected cancer for research purposes.

One of the most important findings we made is that different brain cancers contain very different types of immune landscapes. In particular, we found that specific brain cancers that arise within the brain (called gliomas) have a very distinct immune landscape compared to cancers that develop elsewhere in the body and later spread to the brain (termed brain metastases). We also saw that gliomas contain different immune landscapes depending on the genetic mutations they harbour in their cancer cells (in particular whether they contain a mutated

version of a metabolic enzyme called isocitrate dehydrogenase, “IDH”).

The most striking difference we uncovered was related to the origin of immune cells in brain cancers. Microglia are brain-resident immune cells that perform essential surveillance functions under healthy conditions. They belong to the macrophages family – a large group of immune cells that reside in many organs throughout our bodies. Macrophages play a critical role in clearing invading pathogens and removing dying and malignant cells from organ tissues. However, when cancer develops, their regular functions can become subverted and hijacked, resulting in accelerated cancer growth. While most tissue-resident macrophages, including microglia, are generated during embryonic development, some can alternatively be produced from circulating white blood cells (termed monocytes) upon acute inflammation, but also during cancer development. Interestingly, we found these cells, which we call monocyte-derived macrophages ("MDMs"), at much higher frequencies in brain metastases and gliomas without an IDH mutation (which typically represent higher-grade brain tumours compared to IDH-mutant gliomas). Together, microglia and MDMs were by far the most abundant immune cell population in gliomas.

While MDMs resemble microglia in many aspects, we wondered whether their distinct cellular origin might also convey differences in their functionality. Therefore, we queried the gene expression program of both cell types, and indeed found that they substantially differ depending on where they originate from, but also with regards to the brain cancer type they reside in. This indicates that both nature and nurture can determine the function these cells serve in a specific cancer type. Our findings thereby emphasise the importance of understanding each patients' cancer's unique characteristics and the immune landscape shaping it to develop the most effective (immuno)therapy.

When comparing microglia and MDMs in brain cancers to healthy individuals, we further detected several alterations that indicate their contribution to immunotherapy resistance. This now opens exciting possibilities to explore whether unique functions of these cells may allow us to harness their natural cancer-suppressing capabilities, and thereby improve the response to immunotherapies in certain brain cancer types.

But we did not only uncover significant differences in microglia and MDMs. Compared to gliomas, we found that brain metastases contain a much more diverse immune cell landscape. Brain metastases are populated by vast numbers of other immune cells called neutrophils and T cells. T cells represent an important line of defence against tumour cells as they are capable of sensing and destroying cells undergoing malignant transformation. However, the T cells we found in brain metastases were largely dysfunctional and showed signs of severe exhaustion. Interestingly, when analysing these cancers' spatial organisation, we frequently found T cells in close proximity to microglia and MDMs – hinting at the possibility that those cells may be involved in actively shutting down T cells in brain tumours.

Notably, another research laboratory in Zurich used a completely different experimental strategy to explore immune cells in an independent patient group and reached similar conclusions to our study. Together, these two studies represent the first to chart the complete immune landscape of diverse brain cancers in such a comprehensive manner and pave the way to innovate new therapies to tackle these devastating diseases.