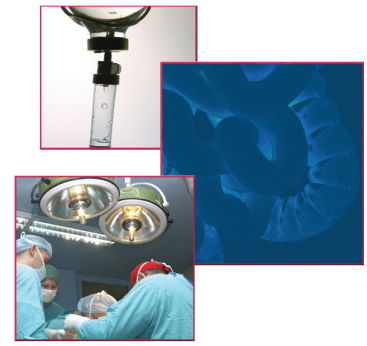
Interview

Colorectal Cancer



The role of colorectal cancer plasticity in metastasis and treatment: an interview with Mirjana Efremova

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Mirjana Efremova speaks to Megan Bryant, Journal Development Editor for *Colorectal Cancer* at the 4th International Cancer Conference at the CRICK Institute about her research into how colorectal cells adapt and change through plasticity.

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Could you please provide a brief overview of your career to date?

I am a computational biologist by training with a PhD in molecular oncology from the Department of Bioinformatics at the Medical University of Innsbruck. During my PhD I investigated how the immune system shapes the evolution of colorectal cancer. At the time, we used bulk omics data. While this was great, questions were still left unanswered because bulk data cannot differentiate between all the cells comprising the tumor and the tumor microenvironment. For my postdoctoral research, I joined Sarah Teichmann's Lab (Wellcome Sanger Institute) which stood at the centre of the innovation in single-cell technologies. There I co-led the development of the first human atlas of the maternal–fetal interface in early pregnancy using single cell transcriptomics. I became interested in understanding how cells communicate and how signals from the environment mediate distinct cellular phenotypes, particularly in cancer and I developed a cell–cell communication statistical framework – CellPhoneDB – for inference of cellular communication networks. Eventually, I established my lab at the Barts Cancer Institute, where we are focused on studying cancer cell plasticity.

Can you please provide an overview of your current research?

Our current research is centered on understanding cancer cell plasticity, which is the ability of cells to switch their state in response to external factors and adapt to new microenvironments such as those encountered during metastasis or in response to therapy. Our aim is to understand the role of plasticity in metastasis and therapy response, examining both intrinsic factors and the influence of the microenvironment.

Could you explain how cancer cell plasticity plays a role in the metastasis of colorectal cancer cells & their resistance to therapy?

In our research so far, we have identified putative pro-metastatic cells in colorectal cancer patient samples that we think are the cells that disseminate and metastasize in the liver. We also have uncovered gene regulatory networks that we think drive those cell states. Using spatial data, we have found specific immunosuppressive and stromal cells that mediate and sustain the pro-metastatic cells.

We have now also established organoids and we are currently working on validating our findings with the goal of developing new therapeutic approaches.

Future Medicine

Are there any notable differences in the mechanisms of cancer cell plasticity between colorectal cancer & other cancer types? How does this inform your research?

While we primarily focus on colorectal cancer, cancer cell plasticity can manifest in different ways in different cancers.

Colorectal cancers have a cellular hierarchy resembling a healthy intestine, maintained by *LGR5* expressing stem cells. However, both in healthy conditions and cancer, lineage tracing studies have revealed a high degree of plasticity. In a healthy intestine, upon tissue damage or ablation of the stem cells, differentiated cells can dedifferentiate into stem cells and repopulate the impaired stem-cell niches and regrow the cancer.

This plasticity is also crucial in metastasis where it has been shown that disseminating cells are actually *LGR5* negative and that they require an *LGR5*+ stem cell phenotype at metastatic sites through plasticity to establish larger macrometastasis. In addition to this, a recent study showed that these *LGR5*- disseminating cells can further differentiate into noncanonical squamous or neuroendocrine-like states in some patients, showing progressive plasticity in metastasis.

Another mechanism of plasticity, transdifferentiation, occurs when differentiated cells from one lineage convert to another. This type of plasticity has been demonstrated in other cancers, for example, in prostate cancer and breast cancer where you have luminal-to-basal conversion. Epithelial-to-mesenchymal transition is another form of plasticity that occurs in colorectal cancer as well as many other cancers. So, we recognize both similarities and specifics tied to the cell of origin of distinct cancers.

You use a number of technologies within your research, could you elaborate on the importance of single cell omics & computational analyses in your research?

Single cell omics are crucial for our research as they allow us to profile heterogeneous cancer cell phenotypes. Genetic clones have been researched a lot in the past, however, we are now investigating phenotypic heterogeneity, as well as epigenetic mechanisms driving this heterogeneity. Single cell technologies also enable us to to model how the cells are transitioning between cell states. In addition, we use single cell data integration with spatial technologies to investigate the spatial organization of cells in tissues, helping us infer cell–cell communication networks. This approach is instrumental in studying phenotypic heterogeneity and nongenetic mechanisms of tumor progression and therapy resistance.

What future directions do you envision for your research, & how do you hope it will contribute to our understanding of colorectal cancer metastasis & therapy resistance, ultimately benefiting patients & clinical practice?

Our immediate goals involve modelling colorectal cancer *in vitro* using patient-derived organoids to manipulate cell states through genetic modification or the addition of ligands in culture to push cells into specific states. We are also focusing on the effect of therapy. Eventually, we aim to expand our research to different cancer types. Ultimately, we hope our work will lead to a better understanding of colorectal cancer, improved treatment strategies, and, most importantly, better outcomes for patients in clinical practice.

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Competing interests disclosure

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