New model aims to promote better-adapted bladder cancer treatment in the future

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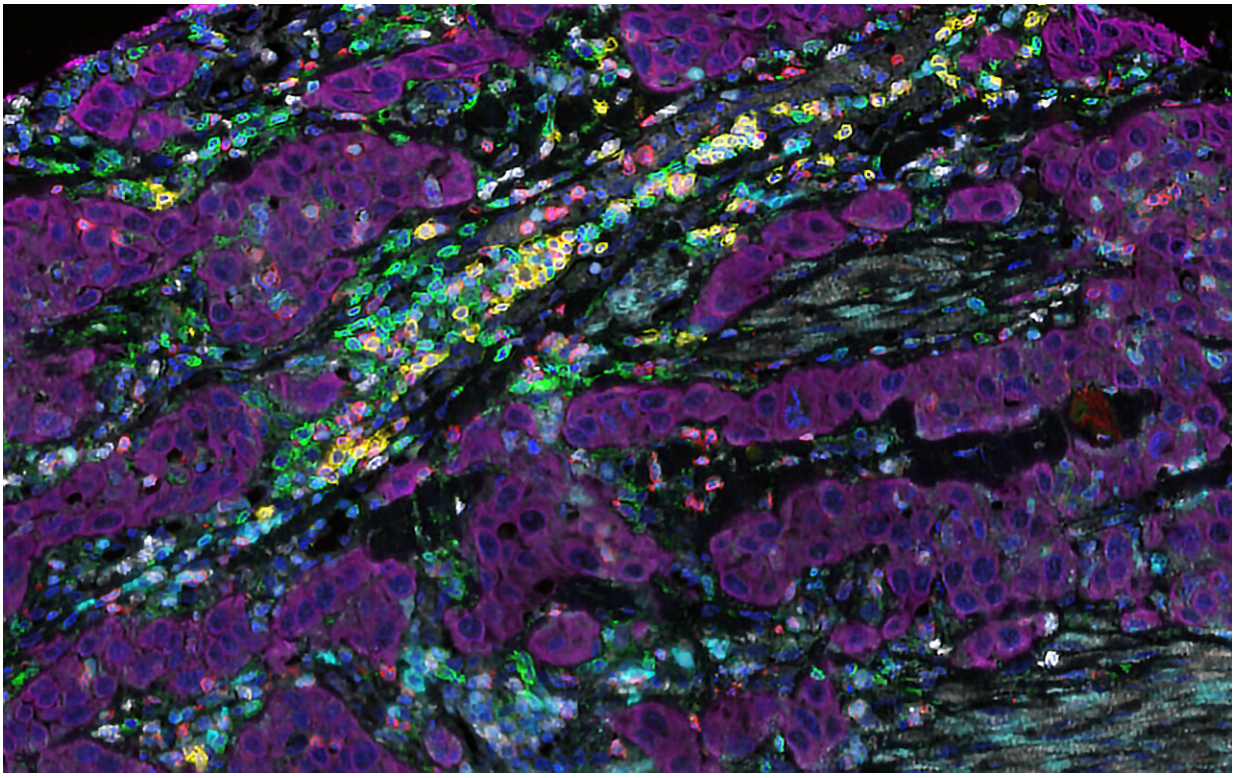

Microscopic image of human tumour tissue (coloured magenta) and various immune cells: T cells (green and red), B cells (yellow) and NK (natural killer) cells (white). Activated T and B cells are depicted in cornflower blue, while the nuclei of all the cells are shown in the darker blue shade. Credit: Iliana Kyriaki Kerzeli

Uppsala University scientists have designed a new mouse model that

facilitates study of factors contributing to the progression of human bladder cancer and of immune-system activation when the tumor is growing. Using this model, they have been able to study how proteins change before, while and after a tumor develops in the bladder wall. The study has now been published in the scientific journal *PLOS ONE*.

"The model was designed both to contain specific oncogenes, as they're called—mutations that can drive tumor growth—and to show a high incidence of harmful mutations, which we often see in people who get bladder cancer. These harmful mutations arise because of smoking, for instance, which is the single biggest risk factor for bladder cancer in the West. In that way, our model imitates how this form of cancer develops in humans," explains Sara Mangsbo, principle investigator and senior lecturer at the Department of Pharmaceutical Biosciences at Uppsala University.

The main challenges in creating the mouse model were, first, to produce an organism with an immune system that functions like the human one, and second, to cause the tumor to grow in the right site and for the same reasons as in us. Previous studies and models have often used female mice as mouse models for bladder cancer, which does not fully reflect what the disease is like in humans, where the cancer is three times as common in men as in women. However, women often have a more aggressive cancer at the time of diagnosis. In the new model, both sexes have been investigated and the data can therefore be used to study how tumors develop in females and males respectively, and how both respond to various treatments.

The scientists have now used the model to take a closer look, in blood and urine, at the proteomic profile (secreted substances from the tumor/immune cell area) when the tumors arise, grow and spread. The investigations included examining more than 90 proteins to find out how these change in the course of tumor development and after the disease

has infiltrated the muscle layer), called muscle-invasive bladder cancer.

How the gene expression in the tumor changed from when it was confined to only one site to when it had infiltrated the tumor was studied through "single-cell sequencing." Thus, the researchers were able to get an idea of which cells were appearing and which were disappearing, how cancer cells and surrounding tissue were interacting and which types of immune cell were being activated.

The scientists noted a distinct gender difference both in the type of bladder cancer that developed in the early stage of the disease, but also that the sexes responded differently to immunotherapy, a form of treatment that activates the immune system to fight tumors.

"In the next phase of the project, the model can give us a better understanding of the types of immune cells that infiltrate the tumors. And we hope that in the future, it will help to improve our knowledge of how to design treatment strategies specifically adapted for men and women. For this to become a reality, studies must also be linked to analyses of clinical material from biobanks," Mangsbo says.

The work of developing the tumor model and studying it at the level of pathology, proteomics and single cells is a collaboration involving the Sara Mangsbo lab at the Department of Pharmaceutical Biosciences; Anca Dragomir, Sven Nelander and Milena Doroszko at Immunology, Genetics and Pathology; and in the lead, Ulrika Segersten and Per-Uno Malmström at Surgical Sciences.

More information: Iliana K. Kerzeli et al. (2021), Single-cell RNAseq and longitudinal proteomic analysis of a novel semi-spontaneous urothelial cancer model reveals tumor cell heterogeneity and pretumoral urine protein alterations, *PLOS ONE*. journals.plos.org/plosone/arti … journal.pone.0253178

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