Tissue structure delays cancer development

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Cancer growth normally follows a lengthy period of development. Over the course of time, genetic mutations often accumulate in cells, leading first to pre-cancerous conditions and ultimately to tumour growth. Using a mathematical model, scientists at the Max Planck Institute for Dynamics and Self-Organization in Gottingen, University of Pennsylvania and University of California San Francisco, have now shown that spatial tissue structure, such as that found in the colon, slows down the accumulation of genetic mutations, thereby delaying the onset of cancer. Their model could help in the assessment of tissue biopsies and improve predictions of the progression of certain cancer types.

Many types of cancer develop unnoticed in the body over a long number of years before the disease erupts. The point of departure is provided by specific genetic mutations including point mutations, copy number alterations, loss of heterozygosity, and other structural rearrangements, that gradually accumulate in the cells, leading to the formation of pre-cancerous lesions. If a certain number of mutations is reached in individual cells, the cells begin to proliferate unchecked. For some cancer types, the accumulation process can take up to 20 years. However, not everyone with pre-cancerous tissue will actually develop cancer; the formation of abnormal cells often has no medical consequences. To date, it is still unclear why tumours develop in some cases and not in others.

Using mathematical modelling, a research group headed by Erik Martens and Oskar Hallatschek of the Max Planck Institute for Dynamics and Self-Organization in Göttingen have studied how genetic mutations

spread, the speed of the mutation accumulation process, and the impact of this process on the progression of pre-cancerous conditions. They have shown that the destiny of oncogenic or cancer-causing mutations depends in part on where they occur and how much competition they are exposed to from other, similar mutations. In an environment without any spatial structure, for example in the blood, genetic mutations can propagate and accumulate relatively fast. In tissue with clear spatial structure, such as that of the colon, however, it takes longer for cells to accumulate the number of mutations required for tumour formation.

The study was based on a theoretical model of evolution developed by the two Max Planck scientists. Many genetic mutations are detrimental to the mutated cells and therefore do not prosper. On the other hand, certain genetic alterations give their hosts a competitive advantage over other cells. This includes, for example, mutations that increase the rate of cell division. "That direct advantage enables cells with this type of mutation to proliferate and accumulate in the tissue; but in such cases, what is advantageous to the cell is harmful to the patient, as it may ultimately cause cancer", explains Erik Martens.

The model used in this research was based on tissue like that of the intestinal wall, which contains many pockets or crypts, each containing isolated groups of cells that may accumulate and carry different mutations. If mutations arise only rarely, they may spread unhindered through the pre-cancerous tissue. However, if other mutations occur before the first one has spread throughout the tissue, the diverse mutation clones meet and compete with one another for survival. In such cases, there are many losers and few winners, and only certain mutations are successful in establishing themselves.

In principle, advantageous mutations cannot proliferate as quickly in spatially structured cell populations as in fully mixed or structureless populations. Consequently, the competition between mutations in

spatially structured tissue is often very strong, and the mutation accumulation rate is lower than in non-structured populations. According to the study, this is why structured populations take longer to reach a critical number of mutations, thereby delaying the onset of cancer.

"Even though many types of cancer arise in body tissues with clear spatial structures, most earlier models of cancer progression neglected this aspect and were based on well-mixed cell populations", explains Erik Martens. "However, it is important to integrate the structural aspect in order to better predict how pre-cancerous conditions progress. For instance, tissue with spatial structure accumulates fewer mutations over a given period than tissue with unstructured cells. It could therefore be that the number of mutations required to trigger certain types of cancer has been overestimated". The researchers hope that their findings will help improve the interpretation of tissue biopsies and contribute to more realistic predictions of cancer progression.

More information: Erik A. Martens, Rumen Kostadinov, Carlo C. Maley and Oskar Hallatschek Spatial Structure Increases the Waiting Time for Cancer, *New Journal of Physics* 13, 115014 (2011), doi: 10.1088/1367-2630/13/11/115014

Background article:
Erik A. Martens and Oskar Hallatschek Interfering Waves of Adaptation Promote Spatial Mixing, *Genetics* 189 (2011), doi: 10.1534/genetics.111.130112

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