Gene duplication explains tumor aggressiveness

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Pancreatic cancer is a form of cancer associated with the highest mortality rates in the world. Genetic changes that could explain its aggressiveness and early metastasis are elusive. A team at Technical University of Munich has now shown that those characteristics can be explained by specific gene amplifications that occur along evolutionary pathways of the cancer. Based on this discovery, they have derived basic principles underlying the biology of pancreatic cancer.

Until now, scientists have failed to establish a link between the properties of pancreatic cancer, such as its aggressiveness, and changes, i.e. mutations, in the tumor's genome. Moreover, pancreatic cancer forms metastases much faster than other types of cancer. Here, too, the genetic causes are unclear.

A team headed by Professor Roland Rad and Professor Dieter Saur of TUM University Hospital has taken an important step toward solving both mysteries. With the help of mouse models for pancreatic cancer, they have determined the molecular pathways of tumor development in detail and gained a better understanding of how characteristics of the disease arise. The study was published in the journal *Nature*.

Healthy cells in humans possess two copies of each gene. For their experiments, the researchers mutated one of the two copies of the KRAS gene in mice. The gene plays a key role in cellular proliferation and is activated in 90 percent of all human pancreatic tumors. Such genes are referred to as oncogenes. The team headed by Roland Rad made a surprising discovery: The mutant gene was often duplicated even in very early stages of the cancer. In cases where a tumor had not doubled the mutated KRAS gene copy, the researchers discovered duplications in other cancer genes.

"It therefore appears that the cell amplifies the growth signal due to the presence of extra gene copies. This model of dosage amplification during tumor development had not previously been considered," says Sebastian Müller, lead author of the study. "We also showed that as the number of mutant KRAS copies increases, the tumor's aggressiveness and ability to metastasize also increases."

Disruption of endogenous protective mechanisms determines the evolution of the cancer

Normally, healthy cells have their own protective mechanisms to prevent mutations from accumulating. So how could the cells develop such dosage amplification without being prevented from doing so?

"This shows the importance of mouse models, which allow us to observe and experimentally review the extraordinarily complex processes of cancer development at the molecular level, from healthy cells to cancer precursors, to aggressive tumors and their spread to other organs," Professor Dieter Saur explains.

After the KRAS mutation was induced by the researchers, other mutations in what are known as tumor suppressor genes developed. A healthy cell possesses a whole series of such protective genes to prevent cancer from developing. A significant finding by the team was that either the mutant KRAS gene or another cancer gene is amplified, depending on which tumor suppressor gene is affected and to what degree its function is impaired.

Key developmental stages explained

Only after the cell's inbuilt protective mechanisms have been switched off and dosage amplification occurs does a tumor ultimately form. Which pathway the cell follows, and which genes are involved then largely determine the characteristics of a pancreatic tumor.

For the first time, the dosage amplification model allows researchers to identify genetic patterns that explain a tumor's aggressiveness and metastasis. "We have indications that our discovery constitutes a fundamental principle in the development of tumors and plays an essential role in other cancers. We're now investigating the extent to which these new insights into cancer biology can be used to develop new therapeutic strategies," says Professor Roland Rad, explaining the team's next research goals.

More information: Sebastian Mueller et al. Evolutionary routes and KRAS dosage define pancreatic cancer phenotypes, *Nature* (2018). DOI: 10.1038/nature25459

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