Kidney cancer: A disease which begins in childhood

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A detailed analysis of the genome from a number of renal cancer patients indicates that these tumors originate from a chromosomal break, which happened during childhood or adolescence, sometimes as many as 50 years prior to diagnosis of the tumor.

RENAL CELL CARCINOMA

Kidney cancer affects about 300,000 people each year worldwide, and nearly half of the patients who develop this disease will die from it. The most common type of renal cancer (between 60 and 80% of all renal cancers) is a form called clear cell renal cell carcinoma (ccRCC), a tumor which develops within the epithelial cells of the renal cortex (external surface of the kidney) and which is characterized by round cancer cells whose liquid interior (cytoplasm) is translucent.

At the molecular level, one of the principal characteristics of ccRCC is the loss of a portion of chromosome 3. This phenomenon is observed in nearly all patients who develop this cancer and certainly plays an important role in the evolution of the disease because this segment of DNA contains several tumor suppressor genes, the best known being VHL (so named because mutations to this gene are responsible for Von Hippel-Lindau disease). As the loss of tumor suppressors is a mechanism involved in the development of several types of cancers, it is thus quite probable that the elimination of this region of chromosome 3 contributes to the development of ccRCC.

CATASTROPHE IN THE CHROMOSOMES

To better understand the sequence of events involved in losing a segment of chromosome 3 and the subsequent evolution of cancer, a team of British scientists at the Wellcome Trust Sanger Institute undertook the Herculean task of completely analyzing the genomic material of 95 biopsy samples removed from different locations in ccRCC tumors present in 33 different patients[1]. They found that, in nearly half of these patients, the missing segment of chromosome 3 had been lost due to a sudden disruption of the chromosome by a phenomenon called chromothripsis (from the Greek *thripsis*, meaning "fall to pieces"). This phenomenon is a real catastrophe where the chromosome is broken into dozens or even hundreds of pieces and cannot be adequately repaired by the cell. In the case of ccRCC, it seems that this fragmentation also occurs while a supplementary copy of chromosome 5 is being made, leading to the creation of a rearrangement where part of chromosome 3 is fused with chromosome 5.

PRECOCIOUS DAMAGE

Using the complex techniques of "molecular archaeology" to estimate the time when the alteration in the cancer cell DNA occurred, the authors discovered that the fusion between chromosomes 3 and 5 occurred quite early in the development of the ccRCC tumors, happening 30 to 50 years before the cancers were clinically detectable. Since the majority of ccRCC are diagnosed around the age of 60, this means that the events triggering these cancers is produced very early in the lives of these patients, during childhood or adolescence.

This very long latency is explained by the fact that, despite the severity of the damage suffered by chromosome 3, this mutation by itself is insufficient to actually trigger the progression of the cancer and the initial expansion of these mutants is limited to about a hundred cells. We have another copy of chromosome 3 which can take over and prevent the development of cancer. According to the authors, it is likely that the majority of us have some of these precancerous cells, without actually developing a renal cancer.

In time, however, the risk of mutation to the second chromosome 3 accumulates and, when such a mutation occurs in the suppressor gene VHL, the tumor can thus begin its actual progression and development into a mature cancer. As is the case for other types of cancer, this long latency nevertheless offers a large window for prevention and it is possible to imagine that we may be able within a few years to develop methods for identifying patients who harbour these immature renal tumors and thus quickly intervene before the cancers reach an advanced stage which is difficult to treat.

While we wait for such new tools to become available, one can recall that certain aspects of lifestyle increase the risk of renal cancer and that modification of these habits could contribute to preventing the occurrence of additional mutations, which would trigger the development of the cancer. One of the best characterized factors is smoking, and there is no doubt that quitting smoking represents a tangible step towards diminishing the risk of renal cancer (just as for lung cancer, bladder cancer and a dozen other types of cancers). Another important factor is excess weight, particularly obesity, which triples the risk of renal cancer possibly because of the excess fat which envelopes the organs of the abdominal cavity (e.g. the kidneys, colon and uterus), providing an environment rich in inflammatory molecules which favor the appearance of mutations and the progression of cancer.

(1) Mitchell TJ et al. Timing the landmark events in the evolution of clear cell renal cell cancer: TRACERx Renal. Cell 2018; 173: 611-623.

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