Carcinogenesis and stem cells replication: a new perspective

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"I like to imagine St. Peter sitting on a stool next to a window in which he can look down, towards the Earth".

The Joke. Milan Kundera. 1984

Cancer is the result of the accumulation of mutations and alterations in the expression of the driver genes, which determine an increase of cellular proliferation. These mutations can have several origins:

1. Environmental: A large number of epidemiological studies have shown that exposure to certain agents may increase the risk of developing cancer.
2. Hereditary: Studies in twins and in families with the same type of cancer have shown that some mutations related to specific types of cancer are hereditary.
3. Errors in DNA replication: recently, it has been highlighted as a new explanation of the origin of the cancer, which would explain why neoplasia is more frequent in some organs than in others[1].

According to Cristian Tomasetti and Bert Vogelstein, every time a normal stem cell (SC) divides, three mutations occur, so the lifetime cancer risk in each tissue correlates significantly with the number of cell divisions that occur in SCs of these tissues. That is, tissues with a high number of divisions of their SCs have an increased risk of developing a neoplasia. Thus, replication errors, according to the authors, are the factor that has the greatest influence on the etiology of cancer: "Many genomic changes occur simply by chance during DNA replication rather than as a result of carcinogenic factors"[1]. These errors occur in the SCs of each tissue, which are in charge of maintaining its architecture, and they are the ones that give rise to tumors.

To test this hypothesis, the authors evaluated the incidence of cancer in 69 countries, with a representation of two-thirds of the world population, subjected to different environmental exposures, evaluating seventeen different tissues from which the number of SCs divisions is known[2]. When correlating the cancer risk in a specific tissue with the number of SCs divisions during the lifetime of that tissue, a high correlation was found, with a mean of 0.8 (between 0.67 and 0.84), and in 89% of countries a correlation greater than 0.7. As the age range evaluated increases, the correlation increases, as the risk of cancer rises exponentially with age, due to the

greater accumulation of SCs divisions. This explains why, in an imaginary population, without hereditary mutations and in an environment without carcinogenic agents, because “error-free replication in incompatible with basic biologic principles of evolution”, near 40% of the mutations would be attributable to replication errors. This means that the tissues that have the greatest number of divisions, that is, greater activity of SCs, would have a greater amount of mutations accumulated with a marked contribution of this factor in the etiology of cancer.

To separate the effects of replication errors from hereditary or environmental factors, the authors propose an additional risk score (ERS), which is the product of the risk of suffering a type of cancer during lifetime by the number of divisions of SCs[1]. If the ERS of a tissue is high, environmental or hereditary factors are expected to have a greater impact on the risk of developing a neoplasia, which is demonstrated in the study because the tissues that resulted in greater ERS were those with well-defined hereditary or environmental factors, such as colon cancer associated with Lynch syndrome, hepatocellular cancer associated with HCV, among others. However, in tumors with low ERS, such as pancreatic cancer, small bowel carcinoma, or non-smokers lung cancer, there appears to be no other environmental or hereditary risk factor, but only replication errors. That is, the development of tumors with low ERS in a patient seems to be due only, in the words of the same authors, to "bad luck".

In cancers whose etiology is involved a virus, like the case of all types of cancer associated with HPV, the proportion of mutations generated by the virus confers a contribution greater than 60%, in the case of cervical cancer and the HPV type 16, i.e., that the environmental origin of this type of cancer has a greater weight than the hereditary origin or of replication. That makes it, as has been demonstrated from the epidemiological point of view, sensitive to primary prevention through vaccination against HPV and the control of other associated environmental risk factors.

In the case of the breast, the contribution of environmental factors is less than 15%, being the replicative origin the etiological factor that generates this type of neoplasia [2]. According to this trial, from a practical point of view, primary prevention does not seem to have much influence, but the detection of cases in initial stages becomes the most appropriate prevention strategy.

At least four sources of mutations are described for replication errors: quantum effects in base pairing, errors made by the polymerase enzymes, hydrolytic deamination of the bases and damage by free radicals generated endogenously. It is unknown whether replication errors, according to these results contributing largely to the development of cancer, are caused by some other random factor, because many elements of the cellular function related to replication need to be elucidated. Probably in the future more factors will be described that predispose some patients to develop this type of cancers that are currently believed to be a product of chance, part of the intense controversy generated by these studies.

The authors rightly conclude that the recognition of a third etiological factor such as replication error mutation “does not diminish the importance of primary prevention but emphasizes that not all cancers can be prevented by avoiding environmental risk factors”. Primary prevention is not the only strategy available to prevent cancer, secondary prevention, i.e. the detection and early therapeutic intervention of a neoplasm, may be the only alternative in cancer due to a higher proportion of mutations by replication errors.

The revolution that these studies have generated should not neglect years of epidemiological research and recommendations in cancer prevention. The real revolution lies in shifting the focus

and selecting which types of cancer are actually susceptible to primary or secondary prevention, and to focus efforts and resources, with real expectations, to work in that direction, as well as to continue to investigate to decipher whether replication errors have a different origin to the evasive chance and that may be susceptible of prevention or treatment.

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