Opinion

Stem Cell INVESTIGATION

Stem cells, environment, and cancer risk

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Understanding the causes of cancer is one key part of the battle against this devastating disease. Environmental and genetic factors are commonly used to explain who gets cancer and in which tissues it develops. A study by Tomasetti and Vogelstein in January this year put forth a third factor—the total number of stem cell divisions in a given tissue—which they believe accounts for the majority of cancer risk (1). The underlying concept is that oncogenic changes to DNA can occur randomly, rather than as a result of environmental factors, and a greater number of cell divisions increase the risk of error. Plotting the lifetime risk of cancer in a particular tissue type against the total number of stem cell divisions in that tissue during the average lifetime of a human, they found a correlation of 0.81, and this correlation extended across five orders of magnitude. This led some in the general public to conclude that cancer is due merely to "bad luck". The study identified cancers that are deterministic (influenced by an environmental component) or replicative (due mainly to random errors and representing the majority of cancers). While deterministic tumors can be prevented by vaccines and lifestyle choices, replicative tumors are best combated through secondary measures such as early detection.

This finding was immediately scrutinized and criticized, especially by the cancer prevention community the World Health Organization's International Agency for Research on Cancer (IARC) "strongly disagrees" with the report's conclusions. IARC Director Dr. Christopher Wild said, "*Concluding that 'bad luck' is the major cause of cancer would be misleading and may detract from efforts to identify the causes of the disease and effectively prevent it*." Rozhok *et al*. also responded to the Tomasetti and Vogelstein study, pointing out that their measurements of stem cell numbers and division rates are not reliable. Additionally, they state that the Tomasetti and Vogelstein study incorrectly assumed that cancers arise only from stem cells; evidence suggests otherwise, as post mitotic cells can be induced by injury or inflammation to reenter the cell cycle and become stem-like cells (2).

A more recent study by Wu *et al*. found that environmental factors do indeed play a major role in cancer development (3). Contrary to the Tomasetti and Vogelstein study, they found that intrinsic risk factors contribute less than ~10–30% to the lifetime risk of cancer development. They point out that the earlier study did not distinguish between the effects of intrinsic (random errors in DNA replication) and extrinsic factors (environmental factors such as ultraviolet radiation, ionizing radiation and carcinogens) on stem cell division. According to their calculations, intrinsic risk is better estimated by the lower bound risk controlling for total stem cell divisions, and intrinsic processes are not sufficient to account for the observed cancer risks. This allowed them to reach the conclusion that cancer risk is heavily influenced by extrinsic factors.

The critical role of genetic and environmental factors in determining cancer risk is supported by overwhelming scientific evidence. At the same time, the stochastic stem cell division factor identified by Tomasetti and Vogelstein is derived from rigorous mathematical modeling. In many respects, their conclusion is refreshing. It stimulates reexamination of many assumptions and theories about the origins and development of cancer and our strategies for prevention, detection, and treatment. It is certainly misleading to conclude that cancer is a result of "bad luck" and that intervention methods are not effective. As indicated in the Tomasetti and Vogelstein paper, the total number of stem cells in an organ and their proliferation rate may of course be influenced by genetic and environmental factors. The "bad luck" factor from stochastic stem cell division

may be controlled by lifestyle choices and thus is not purely bad luck.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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