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Stem cell divisions and cancer

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The intriguing work by Tomasetti and Vogelstein[1] implicates number of stem cell divisions in cancer risk. The authors proposed 'the lifetime risk of cancers on many different types is strongly correlated (0.81) with total number of divisions of normal self-renewing cells maintaining that tissues homeostasis.' Their results suggested that 'only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions.' They focused on the 'extreme variation in cancer incidence across different tissues' and identified 31 tissue types to assess stem cell numbers and proliferative rate. They further clustered cancer types into deterministic or replicative. Deterministic referred to cancers caused by deterministic factors 'such as environmental mutagens or hereditary predispositions.' Replicative referred to cancers related to 'errors during DNA replication.' This, of course, depends entirely on the validity of input data. We recently reported that previous estimates of proliferative rates of bone marrow hematopoietic stem cells are wrong.[2] Prior studies suggested primitive bone marrow stem cells were dormant in G_O, but we found virtually all primitive bone marrow stem cells are proliferating and the previously defined G_0 stem cells rapidly transit cycle *in vivo*.[3] The problem in prior estimates was that most proliferating stem cells were discarded by the standard stem cell purifications.

The bone marrow hematopoietic stem cell is probably the best, most extensively studied stem cell; other stem cell systems are generally poorly defined and determination of their replicative rates borders on the fanciful, including chronic lymphocytic leukemia, Glioblastoma multiforme, head and neck squamous cell carcinoma, lung adenocarcinoma and osteosarcoma. In the latter instance the authors state that 'stem cells divide every 15 years.' This is quite extraordinary. Finally, one might consider that every lymphocyte is a potential stem cell when it encounters its antigen. Altogether estimates of stem cell proliferation in all of these cell systems are unreliable.

Another important consideration is the concept of the immortal strand in stem cell biology. In the 1970s Cairns proposed stem cells maintained genetic constancy through cell division by cosegregating the parental DNA strands into the cell destined to remain a stem cell.[4] This phenomenon was shown experimentally in embryonic fibroblasts[5] and then in intestinal epithelial cells.[6] There was little confirmation of these data until recently when evidence for immortal strand segregation was shown *in vitro* in neurospheres and immortalized mouse

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CONFLICT OF INTEREST

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cancer cell cultures and *in vivo* in intestinal, mammary and muscle stem cells.[7] The immortal strand phenomenon was considered a possible mechanism protecting stem cells from mutations and the development of cancer. Given the rapid proliferative rate of hematopoietic stem cells and the relatively low incidence of acute leukemia, it seems some mechanism, such as immortal strand segregation, must protect against their becoming neoplastic. This adds another confounding aspect to the attempt to estimate cancer risk by stem cell divisions. It is worth noting that data supporting the immortal strand hypothesis indicate many studies using label-retaining cells to estimate stem cell populations are probably wrong.

Finally, the authors underestimated the huge impact of microenvironment on carcinogenesis, the Tissue Organization Field Theory (TOFT).[8] Substantial data suggest the somatic mutation theory of cancer does not explain all, or even most cancers. The capacity of cancers to revert to normal when exposed to different environments represents one dramatic base for TOFT as does the observation break point cluster region/ABL, which characterizes the stem cell disease chronic myelogenous leukemia, is present in ~10% of healthy persons most of whom do not develop chronic myeloid leukemia (CML). It is also worth considering the initial mutation in CML may not be at the stem cell level, another confounder.

In summary, we doubt conclusions in the Tomasetti and Vogelstein report are correct, mostly because there are insufficient or inaccurate data to support these biostatistical analyses. Furthermore, the authors' suggestion prevention measures are not likely to be effective in preventing replicative cancers is not well-based, and could harm some persons at risk.

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