LETTER

Cancer resistance and Peto's paradox

Observing that 2 of 3 humans never develop cancer, Klein (1), in a recent PNAS article, argued that research should focus on cancer resistance genes.

This argument can be extended, first, by reconsidering Peto's paradox from 1975, which noted that, while each cancer is considered to have a single-cell origin, there is no cancer excess in whales composed of 10^{17} cells, as compared to mammal relatives with only 10^9 cells (2–3). One may point to other findings that similarly appear to be in conflict with a major role of the molecular aberrations within the cancer cell, for example that 10^8 tumor cells must enter blood circulation for a clinically relevant metastasis to form (4). Consider also that 3 mutations, on average, are formed each of the 10^{16} times the cell's 3×10^9 DNA base pairs are duplicated during a human lifetime. With a view of single-cell transformation as the cause of cancer, these cellular mechanisms need to be tightly regulated, because an alteration of any of these figures by one tenfold could be sufficient to shift human cancer incidence from 30% to 300%.

Many other major diseases with a frequency similar to cancer, such as cardiovascular and autoimmune disorders, are influenced by complex physiological regulatory webs with strong homology among many mammalian species, rather than by events within a single cell. If this were the case for cancer as well, the Peto paradox and some other perplexing observations would make sense.

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