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Gradual rise in cancer stem cells in the crypt-villous axis of the colon during aging

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A primary conceptual challenge in the study of mammalian aging is the occurrence of disease and the intricate relationship of disease processes to aging. One of the most consistent pathological conditions in the gastrointestinal tract (GI) with advancing age is malignancy, specifically colorectal cancer, the incidence of which increases sharply with aging. Although the underlying cellular and molecular events for the age-related rise in colorectal cancer is not fully understood, we have suggested a role for self-renewing, pluripotent cancer stem/stem-like cells (CSCs) in regulating these processes. In support of this, we have demonstrated that the age-related increase in adenomatous polyps in the colon of humans is associated with a concomitant rise in the expression of several CSC markers such as CD44, CD166 and ESA in macroscopically normal appearing colon. A similar increase in CSCs was also observed in the colonic mucosa of aged Fischer-344 rats. Since CSCs are thought to be the mutated counterpart of normal stem cells, which in the colon are primarily located at the bottom of the crypt, we hypothesize that an age-related increase in mutated CSC gradually replicating and eventually occupying the entire crypt-villous axis will lead to the formation of colon tumor. To test this hypothesis, we isolated mucosal cells from the upper-1/3, middle and lower regions of the colon of young (4-month) and aged (24-months) Fischer-344 rats. The cells isolated from all three regions were subjected to spheroid formation and gene mutation analysis. We observed that mucosal cells from the middle and lower, but not the upper region of the colon from aged rats formed a large number of sphere/spheroid-like structures. These spheroids could be extended to 2nd generation. Mucosal cells from the lower region of the colon of young animals were also able to form a small number of spheroids, but they were much smaller and this formation was not very consistent. No spheroids were formed by cells from the middle and upper regions of young animals. This increased spheroid forming ability of mucosal cells from aged rats was associated with increased expression of CD44 and β-catenin. In contrast, CK-20, a marker of differentiation, was greatly augmented in the middle and upper part of the colon of aged rats, compared to cells from the lower region. Frequency of gene mutation was also higher in colonic mucosal cells from the lower region of the colon of aged than young animals. We conclude that with aging there is a gradual increase in CSCs in the colonic crypt which may partly be response for the age-related rise in colorectal cancer.

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