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DNA demethylation in colon cancer

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DNA hypomethylation increases with patient age and correlates with genomic damage in colon cancer (CC). We proposed a wear and tear model linking aging and cancer by the progressive erosion of genomic DNA methylation, inevitably occurring during aging. Two recent examples of DNA demethylation did not fit the wear & tear model, but added new research avenues. A pericentromeric macrosatellite, named SST1/NBL2, is hypomethylated in 22% of colon cancer (CC) with 7% exhibiting a severe hypomethylation (more than 10%) that co-occurred with TP53 mutations in relatively younger patients. Studying the mechanisms underlying the severe demethylation and its impact in genome stability we found that SST1/NBL2 is expressed as a novel long non-coding RNA, the function of which is under study. In a collaborative study of a cohort of near 1,000 CC patients to search for multiple cancer risk biomarkers, we found that low levels of LINE-1 methylation (a surrogate marker of global methylation levels) correlated with the presence of synchronous CC and were predictive of high risk of developing metachronous tumors. Demethylation levels thus serve as prognostic biomarker for improved identification of individuals at high risk for metachronous CC. Among the patients with enhanced demethylation, those with multiple tumors were younger, supporting a role of genetic factors in the increased risk to develop multiple CC. A long-term ongoing prospective cohort study called Genomes for Life (GCAT) at our institution will be useful to further explore the association between epigenetic alterations and the risk for multiple CC. GCAT was designed to explore the role of epidemiologic, environmental, genomic, and epigenomic factors in the development of cancer and other chronic diseases in Catalonia, Spain. GCAT will have recruited 20,000 participants at the end of 2017 with whole genomes sequenced for 1,000 volunteers.

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