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The epigenetics of colon cancer & the *GCAT |Genomes for Life:* a cohort of the genomes of Catalonia

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We have shown that global DNA hypomethylation increases with patient age and correlates with genomic damage in gastrointestinal cancers (Suzuki et al, *Cancer Cell*, 2006). We proposed a "wear and tear" model linking aging and cancer by the unavoidable progressive erosion of genomic DNA methylation during aging. Recently we found two examples of DNA demethyation that did not comply with the “wear & tear” model, but added interesting research avenues.

1) A pericentromeric macrosatellite, named SST1/NBL2, was found hypomethylated in 22% of colon cancer (CC). Seven percent exhibited a *severe* hypomethylation (more than 10%) that co-occurred with *TP53* mutations in relatively younger patients. Induced-demethylation of SST1/NBL2 macrosatellite is followed by histone modification changes that resemble that of facultative heterochromatin (Samuelsson et al, *Epigenomes*, 2016). 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 that forms perinucleolar aggregates in a tight mirror image structure with SAM68 protein nuclear bodies, the function of which is under study.

2) In a collaborative study of a cohort of near 1,000 CCs searching for biomarkers of multiple CC, we found that low levels of LINE-1 methylation (a surrogate marker of global levels of methylation) correlated with the presence of synchronous CC and were predictive of high risk of developing metachronous tumors (Kamiyama et al., *Oncogene,* 2012). Demethylation levels can be used as a prognostic biomarker for improved identification of individuals at high risk for the development of metachronous CC. Among the patients with this enhanced demethylation, those with multiple tumors were younger. This supports a role of endogenous genetic factors in the increased risk to develop multiple tumors.

The *Genomes for Life* (GCAT) is a long-term prospective cohort study ongoing at our institution that should be useful to further explore the association between epigenetic alterations and the risk for (multiple) CC. The GCAT project aims to explore the role of epidemiologic, environmental, genomic, and epigenomic factors in the development of cancer and other chronic diseases in Catalonia. GCAT has recruited near 20.000 participants at the end of 2017. Volunteers complete a detailed epidemiological questionnaire and undergo anthropometry measurements, and plasma, serum, and white blood cells are collected. The GCAT study has access to the Electronic Health Records (EHR) of the Catalan Public Health Care System. Participants will be followed at least 20 years after recruitment. Genomic and epigenomic analyses are being performed to investigate the association of epidemiologic, environmental and genetic risk factors with (multiple) CC and other cancers and other chronic diseases.

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