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Correlation between tumor history and microenvironment using multiregion single-molecule epigenomic data from colorectal cancer patients.

Jose Luis Soto[1] , Sonia Prado[1] , José Manuel Cameselle[2] , Manuel Megías[1] , Diana Valverde[1] , David Posada[1]

1) Department of Biochemistry, Genetics and Immunology and Biomedical Research Center (CINBIO), University of Vigo, Spain. 2) Clinical University Hospital & University of Santiago de Compostela, Santiago de Compostela, Spain.

Colorectal tumors evolve as clonal expansions resulting in accumulation of relatively symmetric masses of cancer cells. However, the genotypic and phenotypic architecture of these bulks is not homogeneous: tumor development leads to intratumor diversity, involving the interplay between cancer subclones and the local microenvironment. Understanding how a single transformed human cell grows into a visible tumor and its connection with an heterogeneous microenvironment is key to understand tumor progression and adaptation. Due to the impracticability of performing serial observations to monitor tumor growth and diversification, the comparison of contemporaneous DNA sequences from different tumor regions becomes a powerful approach to decipher the life history of tumors. However, genomic mutation rates are usually quite low, requiring the study of whole genomes in order to obtain hundreds or thousands of variants amenable to robust phylogenetic analyses. Alternatively, recent studies have shown that DNA methylation changes (with a 10.000-fold higher mutation rate) can also be used as markers of tumoral cell fate to infer clonal expansion dynamics and the time between tumor initiation, invasion and metastasis.

In this study we intend to analyze single-molecule epigenomic data from 12 multiregion samples of 2 colorectal cancer patients. We have generated targeted next generation bisulfite sequencing (TNBS) for the loci IRX2 (201 bp); ZNF454 (200 bp); SLC5A7 (111 bp); CSX (200 bp); and MYOD1 (127 bp) along different hierarchical geographical levels (isolated colorectal glands, tumor regions and primary tumor) to describe tumor population structure, to reconstruct the tumor phylogeny and to estimate relative and absolute mitotic ages for the sampled regions. Finally, we will test whether methylation diversity is correlated across different tumor regions with environmental data derived from immunohistochemical expression of relevant proteins related to morphological differentiation, oxygen levels, rate of cell proliferation, drug resistance or progression. The results obtained will help us understand the potential of epigenomic data to explain tumor adaptation to a dynamic, personalized microenvironment.