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Biography

Manuel Perucho University of Madrid, held faculty appointments at State University of New York (SUNY) Stony Brook. From 1995-2009 was professor and program director, Sanford-Burnham-Prebys Medical Discovery Institute (SBP) La Jolla, California, where he holds an adjunct professor appointment. He was director of the Institute of predictive & personalized medicine of cancer (IMPPC) (2009-2016), and currently is director, program of predictive & personalized medicine of cancer (PMPPC), Institute Germans Trias I Pujol (IGTP), Barcelona, Spain. He was awarded an AACR professorship in basic cancer research, serves in editorial boards of several journals, and reviewed research grants of many agencies and hundreds of papers of over 60 journals.

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THE GENETICS-EPIGENETICS CHRONOLOGIES AND HIERARCHIES IN COLON CANCER

The cancer cell genome accumulates numerous genetic and epigenetic alterations. We showed that a subset of colon cancers (CC) display a mutator phenotype because they harbor hundreds of thousand of somatic mutations simple repeats or microsatellites. Microsatellite instability (MSI) is diagnostic of a distinct molecular pathway for CC as these tumors are very different in genotype and phenotype compared with those without MSI. MSI has become a robust and widely used marker with applications in diagnosis and prognosis of hereditary and non-hereditary CC. Increased DNA hyper methylation was postulated to be the result of a CpG Island methylator phenotype ("CIMP") and underlies the tumorigenesis of some colon cancers when the mismatch repair gene MLH1 is silenced, causing MSI. We showed that the genetic alterations (MSI) supersede the previous epigenetic alterations ("CIMP") in tumor phenotype in colon cancer. The same conclusion is reached when using the recent data from the cancer Genome Atlas (TCGA) consortium. Among the genes frequently hyper methylated are the ADAMTS, encoding extracellular matrix metallopeptidases. Epigenetic silencing of ADAMTS genes in CC takes place in a coordinated manner, not only in cis (linearly linked), but also in trans (in different chromosomes). This is not due to "CIMP" because does not associate with right colon and BRAF mutations, and few of the ADAMTS genes are polycomb repressor complex (PRC) targets, landmarks of the CIMP tumors. We also showed that both hyper methylation and hypo methylation of DNA increase with age of colon cancer (CC) patients. In addition, we showed that hypo methylation (in contrast with hyper methylation) correlates with genomic damage and, in turn, represents a survival biomarker in patients: the greater the hypo methylation the worse the survival, both in gastric cancer and CC. This allowed us to propose a "wear and tear" hypothesis linking aging, gradual demethylation of the genome, genomic instability, and gastrointestinal cancer.

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