

Characterization of human isogenic epithelial cell lines as a relevant tool to study colon carcinogenesis and interaction between genes and environment

Tête A^{1,*}, Arnaud L^{2,*}, Le Mentec H^{3,*}, Gallais I³, Tournadre N³, Duarte-Hospital C^{1,2}, Lippi Y², Mathevet F^{4,5}, Lefort G^{4,5}, Burel A⁶, Surya R⁷, Boutet-Robinet E², Shay JW⁸, Vialaneix N^{4,5,#}, Bortoli S^{1,#}, Lagadic-Gossmann D^{3,#}, Huc L,[#]

¹Inserm UMR S-1124, Université de Paris, 75006 Paris, France

²INRAE UMR 1331 ToxAlim (Research Center in Food Toxicology), Université de Toulouse ENVT, INP, UPS, 180 Chemin de Tournefeuille, France

³Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, France

⁴INRAE, UR875 Mathématiques et Informatique Appliquées Toulouse, F-31326 Castanet-Tolosan, France

⁵Platform Biostatistique, Genotoul, Toulouse, France

⁶Univ Rennes, Biosit - UMS 3480, US_S 018, F-35000 Rennes, France.

⁷Department of Food Technology, Faculty of Engineering, Bina Nusantara University, Jakarta 11480, Indonesia

⁸Department of Cell Biology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, 75390-9039, USA

*Equal contribution; # equal supervision

Colorectal cancer (CRC) is the fourth most common cause of death from cancer worldwide. CRC is a multistep and progressive disease where genetic factors are important in the initiation, the development and the progression of the disease. Then, CRCs can arise from sequential steps including the acquisition of mutations in the adenomatous polyposis coli (*APC*), followed by the mutational activation of oncogene *KRAS* and the inactivation of the tumor suppressor gene, *TP53*. The occurrence of colorectal cancer is largely influenced by the environment, including food contaminants, lifestyle and nutrition. However, the influence of mutations on the response to environmental pollutants is poorly evaluated. Environmental carcinogenesis lacks robust models to explore the interaction between genes and environment and to determine whether genetic mutations associated with colon carcinogenesis generate a particular susceptibility to the harmful effects of pollutants.

Here, we outline the characterization of an innovative cellular model that consists in 6 human isogenic epithelial colon cell lines bearing mutations on master genes involved in CRC. Altogether, these cell lines recapitulate colon carcinogenesis from the healthy, preneoplastic, adenoma and carcinoma stages. We aim to perform a complete phenotypic and metabolic description of these cell lines, with a particular focus on their ability to express the battery of detoxification enzymes, to have a differential sensitivity to genotoxicity, oxidative stress and cell death stimuli, to display a flexible energy metabolism, to migrate and grow without anchorage.

We show that these models of human isogenic colonic cells of CRC could be a powerful and relevant tool to study the effects of environmental pollutants on the colorectal carcinogenesis from the early to the late and metastatic stages and to evaluate gene-environment interactions in food toxicology