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Human colorectal cancer initiation is bidirectional, and cell growth, metabolic genes and transporter genes are early drivers of tumorigenesis

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The role of stem cells in the development of solid tumors remains controversial. In colorectal cancers (CRC), this is complicated by the conflicting “top-down” or “bottom-up” hypotheses of cancer initiation. We profiled the expressions of genes from the top (T) and bottom (B) crypt fractions of normal-appearing human colonic mucosa (M) at least 20 cm away from the tumor as a baseline and compared this to the genes of matched mucosa adjacent to tumors ($M_T$) in twenty-three sporadic CRC patients. In thirteen patients, the genetic distance (M-$M_T$) between the B fractions is smaller than the distance between the T fractions, indicating that the expressions diverge further in the top fractions (B<T). In the remaining patients, the reverse effect is observed (B>T). Assuming that a greater genetic divergence in the top or bottom fractions indicates that position as the initiation site, it is thus equally likely that human CRC initiates from ‘top-down’ via de-differentiated colonocytes or ‘bottom-up’ via dysregulated intestinal stem cells. Dysregulated genes that persist until tumor stage are not limited to tumor suppressors or oncogenes but include metabolic and transporter genes such as *CA7*, *PHLPP2*, and *AQP8*.