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Evolution of the bladder cancer genome from field effects

We developed a strategy that combines histologic and genetic mapping that permits interrogation of the chronology of genetic changes associated with cancer development on a whole-organ scale. By using this approach, we analyzed the sequence of genetic alterations contiguous to the tumor suppressor *RB1* and identified a set of alternative target genes that we term "forerunner" (FR) genes whose silencing was associated with development of clonal plaque-like mucosal field effects initiating bladder carcinogenesis.

Expression and methylation studies identified five candidate FR genes (*ITM2B, LPAR6, MLNR, CAB39L,* and *ARL11*). *In vitro* mechanistic studies demonstrated that three of these genes (*ITM2B, LPAR6* and *ARL11*) control cell survival and proliferation consistent with their loss of function being contributory to tumorigenesis. Whole genome analyses of the field effects revealed a sequential accumulation of alterations in RHO/RAC/Cdc42 pathways that control invasion and cell motility.

These studies identify FR genetic alterations as one of the earliest events in carcinogenesis and provide comprehensive description of field cancerization. The results have important implications for the development of novel detection markers and chemoprevention therapeutic strategies.

Biography

Bogdan Czerniak, MD, Ph.D. is a Professor in the Department of Pathology at UT MD Anderson Cancer Center. His laboratory is credited with the development of a mapping strategy which has provided unique information on the events associated with the development of field effects initiating carcinogenesis. Dr. Czerniak has published over 160 articles in major journals such as Nature, Cancer, Cancer Cell, JNCI, Cancer Research and Plos One.

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