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Aberrant genome duplication as both a cause and a cure for cancer

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Most cancers result from the accumulation of genetic mutations that occur during proliferation of the cells that give rise to and maintain tissues. Cancer driver mutations initiate carcinogenesis, but genome destabilizing mutations promote aneuploidy, which contributes to tumor heterogeneity, drug resistance and treatment failure. Aneuploidy results from missegregation of chromatids during mitosis, which is promoted by aberrant genome duplication in the form of unscheduled endoreplication. At least 35 genes are essential to prevent endoreplication during mitosis and cytokinesis. Fourteen of these genes have been shown to prevent aneuploidy and tumors in mice. Thus, reducing expression of a gene essential to prevent endoreplication during cell proliferation facilitates the rise of cancer. Conversely, induction of aneuploidy can also prevent tumor formation. During mammalian development, pluripotent stem cells give rise to all cell lineages, but when they mislocate to ectopic sites, pluripotent stem cells act as cancer stem cells by producing germ cell tumors. Geminin is one of seven proteins that are essential to prevent DNA re-replication dependent apoptosis during cell proliferation. Although geminin is essential in cells derived from various human cancers, geminin is not essential in normal cells-with one exception. Geminin is essential to prevent DNA re-replication dependent apoptosis in pluripotent embryonic stem cells. Therefore Geminin is a potential chemotherapeutic target in the treatment of germ cell neoplasia, as well as any cancer whose origin depends on a pluripotent progenitor cell.

Biography

Melvin L DePamphilis received his PhD in Biochemistry from the University of Wisconsin, with Post-doctoral work in enzyme mechanisms at UW and tumor virus DNA replication at Stanford University Medical School. He is currently working as a Senior Research Scientist at the National Institutes of Health. Prior to that, he was a Professor in the Department of Biological Chemistry at Harvard Medical School, and then a Lab Chief at the Roche Institute of Molecular Biology. His professional career is focused on genome duplication in animal viruses, cells and preimplantation embryos. He has published 147 research papers, 55 reviews, and 10 books.

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