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Signaling to anchorage-independence in cancer cells

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Anchorage independence is an essential characteristic of metastasizing cells. While normal non-hematopoietic cells undergo programmed cell death (anoikis) consecutive to losing contact with their substratum, cancer cells can survive in the circulation for extended periods of time. In fact, the major limiting factor in the process of metastasis formation is the death of the tumor cells before their implantation in the target organs. Therefore, anchorage independent survival may be more critical to the process of cancer metastasis than organ-specific homing. The metastasis gene osteopontin is expressed at high levels by various cancers and contributes importantly to their progression. In humans, there exist two osteopontin splice variants with deletions of exon 4 (referred to as osteopontin-c) or 5 (called osteopontin-b). The full-length gene product, osteopontin-a, induces a gene expression profile that is associated with tissue remodeling and directed movement/sprouting. It upregulates the levels of glucose in breast cancer cells. This occurs via signals through STAT1 and STAT3 to sn-glycero-3-phosphocholine, and the transcriptional STAT3 targets apolipoprotein D and IGFBP5. Osteopontin-c upregulates intermediates and enzymes in the hexose monophosphate shunt, glycolysis, the glycerol phosphate shuttle, and the mitochondrial respiratory chain. It is associated with elevated cellular ATP levels. The osteopontin-c effect is consistent with the stimulation of an accelerated energy metabolism that is required for anti-anoikis. The splice variants osteopontin-a and osteopontin-c may synergize, with each form activating signal transduction pathways that are distinct from the other. The elevated glucose induced by osteopontin-a is used by osteopontin-c dependent signals to generate chemical energy.

Biography

Georg F. Weber attended medical school in Wuerzburg, Germany. He worked at the Dana-Farber Cancer Institute, Harvard Medical School from 1990 through 1999 and is currently on the faculty at the University of Cincinnati. He has published over 70 scientific reports, including many in the most respected professional journals, and various monographs, most recently a textbook on molecular oncology. He holds several patents. As a component of his mission to research cancer dissemination, he is the founder and chief executive officer of MetaMol Theranostics, a company specialized in diagnosis and treatment of cancer metastasis.

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