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Osteopontin splice variants in cancer dissemination

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In cancer, metastases manifest clinically at advanced disease stages. The dissemination of the transformed cells is an integral characteristic of malignancies and is absent from benign growths. While the major limiting factor in cancer spread is the death of the tumor cells before their implantation into target organs, a fraction of the released cells can survive in the circulation for extended periods of time. The molecular programs of metastasis act to promote tumor progression, not growth or extension of life span. Besides inducing directed migration and invasion, they support adhesion-independent survival. The cytokine Osteopontin is a metastasis gene product that supports the progression of over 30 aggressive tumors. The protein exists in three splice variants, dubbed Osteopontin-a (full-length), -b (lacking exon 5), and -c (lacking exon 4).

1. Untransformed non-hematopoietic cells undergo programmed cell deathconsecutive to losing contact with their substratum. Anchorage-deprivation causes impairment in glucose transport, a deficit in ATP availability and consecutiveanoikis. In cancer cells that have been shed from the primary tumor, metastasis gene products support enhanced energy generation and survival. Variant forms of Osteopontin act as autocrine inducers. Osteopontin-a increases the levels of glucose in deadherentbreast cancer cells. Osteopontin-c, upregulates peroxides as well as intermediates of the hexose monophosphate shunt and glycolysis, which utilize the available glucose and can feed into the tricarboxylic acid cycle. Consecutively, the cellular ATP levels are elevated and the cells can survive.
2. Osteopontin-c is present in 75-80% of breast cancers and 0% of normal breast tissues. It increases with tumor grade. In early breast cancer, high staining intensity of nuclear Osteopontin-c is strongly associated with mortality. Osteopontin-c is not correlated with proliferation markers, ER, PR, or HER2. Bya real-time RT-PCR test,the elevation in Osteopontin-c in the blood detectsa fraction of breast cancers, suggesting prognostic potential of a blood test. Cytosolic staining for exon 4, reflective of Osteopontin-a and -b also predicts poor outcome.In therapy responses, exon 4 is associated with a favorable response to tamoxifen, but a poor response to chemotherapy with CMF (cyclophosphamide, methotrexate, fluorouracil). Osteopontin-c falls short of being a significant predictor for sensitivity to the treatments investigated. The addition of Osteopontin splice variant immunohistochemistry to standard pathology work-ups has the potential to aid decision making in breast cancer treatment.

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Biography:

Georg F. Weber attended medical school in Würzburg, 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. Georg F. Weber has published about 90 scientific reports, including many in the most respected professional journals, as well as various monographs, including textbooks on molecular oncology and anti-cancer drugs. He holds several U.S. and international patents.