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Genetic programs of cancer progression

etastasis formation is an essential aspect of cancer. While the organ preference for dissemination is governed to some degree by tumor-host interactions, there is an intrinsic genetic basis underlying the ability of cancer cells to disseminate to specific distant sites. Metastasis genes are comprised of developmentally non-essential stress response genes, which encode homing receptors, their ligands and extracellular matrix-degrading proteinases. They jointly cause invasion and anchorageindependence. Metastatic potential is conferred to cancer cells by aberrant expression or splicing of these genes, which include osteopontin. The osteopontin gene product is subject to alternative splicing, which yields three RNA messages, osteopontin-a (full length), osteopontin-b (lacking exon 5) and osteopontin-c (lacking exon 4). The shorter forms -b and -c are differentially expressed in cancers, but are absent from healthy tissues. The major limiting factor in the process of metastasis formation is the death of the tumor cells before their implantation in target organs. Hence, anchorage-independent survival is required for cancer spread. The detachment of mammary epithelial cells prompts a loss of glucose transport and resulting ATP deficiency, thus compromising the energy metabolism and causing apoptosis. In invasive breast tumor cells, osteopontin-A and osteopontin-C synergize in supporting tumor progression via up-regulating the energy production, which leads to deadherent survival. Osteopontin splice variants hold promise as potential drug targets. While aberrant expression or splicing of metastasis genes conveys to cancers the ability to break through tissue barriers and disseminate, the genetic basis for organ preference in cancer spread has remained incompletely understood. Metastases are generally characterized by a gene expression core program associated with tissue remodeling (a stress response) that distinguishes metastases from their originating primary tumors as well as from their target host tissues. Site-selectivity is accomplished through a specific program component that adjusts to the target micro-environment. It remains to be investigated whether the gene expression profile of metastases precedes implantation and thus determines organ preference or is shaped by the target site and is thus a consequence of implantation. Chemotherapy of metastatic cancer might be more efficacious if selected to match the genetic makeup of the metastases rather than the organ of origin by the primary tumor.

Biography

Georg F Weber has attended Medical School in Wurzburg, Germany. He worked at the Dana-Farber Cancer Institute, Harvard Medical School from 1990 to 1999 and is currently, working as a Faculty at the University of Cincinnati. He has published close to 100 scientific reports, including many in the most respected professional journals and various monographs, including textbooks on molecular oncology and anti-cancer drugs. His research has made key contributions to understanding the molecular mechanisms of metastasis.

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