

Stem Cell Research 2016_ Mechanisms of cancer progression: Roles of osteopontin variants_ Georg F Weber_ University of Cincinnati Academic Health Center _ USA

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Metastasis formation is an essential aspect of cancer. While the organ preference for dissemination is essentially governed by tumor-host interactions on the epigenetic level, there's a genetic basis underlying the power of cancer cells to disseminate. 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 anchorage independence. Metastatic potential is conferred to cancer cells by aberrant expression or splicing of those genes which include variant CD44 and osteopontin. The CD44 dependent spread of tumor cells is mediated by its cytokine ligand osteopontin which induces directed migration. A C-terminal osteopontin domain ligates the variant exon 6 of CD44 through a protein-protein interaction and is probably going to bind to variant exon 3 through a heparin bridge. Osteopontin is expressed at high levels by various cancers and contributes importantly to their invasive potential. In contrast, osteopontin derived from host cells induces cellular immunity and will bolster anti-tumor protection by cytotoxic T-lymphocytes. Underlying the functional differences between tumor derived and host derived osteopontin are structural characteristics. 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 essential for metastasis. While untransformed non-hematopoietic cells undergo anoikis consecutive to losing contact with their substratum, cancer cells can survive within the circulation for extended periods of your time . The detachment of mammary epithelial cells prompts a loss of glucose transport and ATP deficiency, thus compromising the energy metabolism. Invasive breast tumor cells abundantly express two splice variants of the metastasis gene osteopontin. The osteopontin-a and osteopontin-c synergize in supporting tumor progression via up-regulating the energy production which results in deadherent survival. Osteopontin splice variants hold promise as potential drug targets. OPN may be a highly charged , extracellular matrix protein that lacks an in depth secondary structure. It is composed of about 300 amino acids (297 in mouse; 314 in human) and is expressed as a 33-kDa nascent protein; there also are functionally important cleavage sites. OPN can undergo posttranslational modifications, which increase its apparent

relative molecular mass to about 44 kDa. The OPN gene consists of seven exons, 6 of which containing coding sequence. The first two exons contain the 5' untranslated region (5' UTR). Exons 2, 3, 4, 5, 6, and seven code for 17, 13, 27, 14, 108 and 134 amino acids, respectively. All intron-exon boundaries are of the phase 0 type, thus alternative exon splicing maintains the reading frame of the OPN gene. Regulation of the osteopontin gene is incompletely understood. Different cell types may differ in their regulatory mechanisms of the OPN gene. OPN expression in bone predominantly occurs by osteoblasts and osteocytes (bone-forming cells) also as osteoclasts (bone-resorbing cells). Runx2 (aka Cbfa1) and osterix (Osx) transcription factors are required for the expression of OPN. Runx2 and Osx bind promoters of osteoblast-specific genes such as *Coll1 α 1*, *Bsp*, and *Opn* and upregulate transcription. Hypocalcemia and hypophosphatemia (instances that stimulate kidney proximal tubule cells to produce calcitriol (1 α ,25-dihydroxyvitamin D₃)) lead to increases in OPN transcription, translation and secretion. This is thanks to the presence of a high-specificity vitamin D response element (VDRE) within the OPN gene promoter.