

# 5<sup>th</sup> World Congress on **Cell & Stem Cell Research**

March 23-25, 2015 DoubleTree by Hilton Chicago - North Shore, USA

## Regulation of anchorage-independence by splice variants of osteopontin

Georg F. Weber<sup>1</sup>, Zhanquan Shi<sup>1</sup>, Bo Wang<sup>2</sup>, Tafadzwa Chihanga<sup>2</sup>, Mana Mirza<sup>1</sup> and Michael A. Kennedy<sup>2</sup>

<sup>1</sup> University of Cincinnati Academic Health Center, USA

<sup>2</sup> Miami University, USA

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 in the circulation for extended periods of time. The detachment of mammary epithelial cells prompts a loss of glucose transport, leading to ATP deficiency, compromised energy metabolism, and cell death. Invasive breast tumor cells abundantly express two splice variants of the metastasis gene osteopontin. Osteopontin-a and osteopontin-c synergize in supporting tumor progression via up-regulating the cellular energy production, thus supporting deadherent survival.

Osteopontin-a increases the levels of glucose in breast cancer cells, likely through sn-glycero-3-phosphocholine, STAT3 and its transcriptional targets apolipoprotein D and IGFBP5. Osteopontin-c signaling activates three interdependent pathways of the energy metabolism, comprising the hexose monophosphate shunt and glycolysis that can feed into the tricarboxylic acid cycle, the glycerol phosphate shuttle that supports the mitochondrial respiratory chain, and elevated creatine that increases the formation of ATP. Metabolic probing identified differential regulation of the pathway components, with mitochondrial activity being redox dependent and the creatine pathway depending on glutamine. These molecular connections generate a flow toward two mechanisms of ATP generation, via creatine and via the respiratory chain, which are consistent with a stimulation of the energy metabolism that supports anti-anoikis.

Osteopontin-c is never expressed without the full-length form osteopontin-a. Each of these splice variants activates signal transduction pathways that are distinct from the other. Our findings imply a coalescence in cancer cells between osteopontin-a, which increases the cellular glucose levels, and osteopontin-c, which utilizes this glucose to generate energy. The splice form-specific metabolic effects of osteopontin add a novel aspect to the pro-metastatic functions of this molecule. It is likely that metabolic responses to environmental cues are more common in cell biology than has hitherto been recognized.

### 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. Georg F. Weber has published close to 90 scientific reports, including many in the most respected professional journals, and various monographs, most recently textbooks on molecular oncology and anti-cancer drugs. He holds several patents. As a component of his mission to research cancer dissemination, Georg F. Weber is the founder and chief executive officer of MetaMol Theranostics, a company specialized in diagnosis and treatment of cancer metastasis.

[webergf@UCMAIL.UC.EDU](mailto:webergf@UCMAIL.UC.EDU)

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