

From Biomarkers to Companion Diagnostics: Mitochondrial Metabolic and Apoptogenic Proteins as Predictive and Prognostic Biomarkers

Even in the presence of oxygen, most cancers rely on glycolysis as the main pathway for generating energy (the Warburg effect) and as a source of precursors for generating proteins, nucleotides and lipids. Such metabolic re-programming of cancer cells includes marked over-expression of the isoforms of the mitochondrial-bound glycolytic protein hexokinase (HK), required for energy production. HK also acts as an anti-apoptotic protein via a direct association with VDAC1 localized at the outer mitochondrial membrane and functioning as a gatekeeper for the entry and exit of mitochondrial metabolites, thereby controlling crosstalk between mitochondria and the rest of the cell. VDAC1 also plays a key role in mitochondria-mediated apoptosis through its participation in the release of mitochondrial pro-apoptotic proteins to the cytosol (e.g. cytochrome c, AIF, Smac/DIABLO) and via its interaction with anti-apoptotic proteins, such as members of the Bcl-2 family of proteins. Thus, VDAC1 appears to represent a convergence point for a variety of cell survival and death signals. In our studies, we observed the over-expression of VDAC1, of several of its associated proteins and of other apoptosis-modulating proteins in several cancers. These findings led to the development of a bioenergetics and apoptotic index, reflecting the metabolism and apoptosis reprogramming of the cancer cell that can be considered as a predictive and prognostic biomarker, reporting on disease progression and serving as a treatment therapeutics index.

The Technology

Analyzing the expression profiles of several proteins involved in the metabolic re-programming of cancer cells we found that in certain non-solid as well as solid tumors there is an overexpression of a number of VDAC1 associated proteins such as MAVS (the mitochondrial antiviral-signaling), SMAC/DIABLO (second mitochondria-derived activator of caspases), AIF (apoptosis-inducing factor), HK. Binary logistic regression analysis revealed the ability to predicate the probability of disease based on either VDAC1, Bcl2, SMAC/Diablo, MAVS or a combination of AIF and HK-I expression levels. Moreover, the expression profiles of these proteins point to a cancer survival strategy involving anti-apoptotic defense mechanisms and thus, a lowered susceptibility to apoptosis-mediated cell killing compounds. These protein expression profiles can serve for diagnosing cancer, predicting cancer development and selecting and monitoring response to treatment.

Applications

- Blood tests for early diagnosis, selection and monitoring of treatment in Lymphoma and Leukemia patients
- Solid tumor biopsy profiling for diagnosis and for selecting and monitoring treatment in various cancers, including lung, ovary, prostate, glioblastoma and cervix cancer and melanomas
- Developing a metabolic and apoptotic indices of certain cancers to predict cancer development, and for selecting and monitoring treatment

Advantages:

The proteins identified in our studies as highly expressed in cancer can serve as indicators of the disease state, allowing for early and accurate diagnosis of a number of different cancers and the for the establishment of a therapeutic cellular index for prognosis, for guiding treatment and for assessing effectiveness, all important steps on the road to **tailored personalized therapy**.

Patent Status

Pending

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