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Inhibition of transketolase by oxythiamine altered dynamics of protein signals in pancreatic cancer cells

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Oxythiamine (OT), an analogue of anti-metabolite, can suppress the nonoxidative synthesis of ribose and induce cell apoptosis by causing a G1 phase arrest *in vitro* and *in vivo*. However, the molecular mechanism remains unclear yet. In the present study, a quantitative proteomic analysis using the modified SILAC method (mSILAC) was performed to determine the effect of metabolic inhibition on dynamic changes of protein expression in MIA PaCa-2 cancer cells treated with OT at various doses (0 μM, 5 μM, 50 μM and 500 μM) and time points (0 h, 12 h and 48 h). A total of 52 differential proteins in MIA PaCa-2 cells treated with OT were identified, including 14 phosphorylated proteins. Based on the dynamic expression pattern, these proteins were categorized in three clusters, straight down-regulation (cluster 1, 37% of total proteins), upright "V" shape expression pattern (cluster 2, 47.8% total), and downright "V" shape pattern (cluster 3, 15.2% total). Among them, annexin A1 expression was significantly down-regulated by OT treatment in time-dependent manner, while no change of this protein was observed in OT dose-dependent fashion. Pathway analysis suggested that inhibition of transketolase resulted in changes of multiple cellular signaling pathways associated with cell apoptosis. The temporal expression patterns of proteins revealed that OT altered dynamics of protein expression in time-dependent fashion by suppressing phosphor kinase expression, resulting in cancer cell apoptosis. Results from this study suggest that interference of single metabolic enzyme activity altered multiple cellular signaling pathways.

Biography

Jing Xiao, Professor and Director of the Functional Genomics and Proteomics laboratories at the Alegent Creighton University Medical Center, is an internationally recognized expert in the field of proteomics and metabolomics of cancers and bone disease. He earns his Ph.D. in molecular computational biology about a dozen years ago, focusing on structural modeling of ligand-enzyme interaction and prediction of protein refolding pathways during protein translational process. His research is highly focusing on functional genomics & proteomics analyses of complex disease Including osteoporosis and cancer (especially, breast cancer, pancreatic cancer and prostate cancer). With the established new functional genomics and proteomics platform, he has established several projects covering function of microRNA in estrogen signaling, functional proteomics (focusing on the role of protein posttranslational modifications in cancer and osteoporosis), and proteomics technology development.He has been regular reviewer or *ad hoc* reviewer for several medical journals, different funding agency such as NIH and several journal editorial board members.

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Energy management: A critical role in cancer induction?

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The variety of genes implicated in cancer induction is extensive but paradoxically all cancer cells behave in an identical and highly predictable fashion. This behaviour is closely correlated with a group of cellular morphological criteria termed anaplasticity which involves increases/changes in: motility; invasion; replication; nuclear and chromosomal fragmentation; structural degradation; and phenotypic fluidity. Anaplasticity is so predictive it is a universal clinical yardstick for assessment and treatment. To understand this paradox, perceived mechanisms of cancer induction are reviewed and a new proposal made, namely that cancer is a diversion of energy required for structural organisation into maximum energy dissipation (entropy) through increased dynamic activities. This process is driven by oncogenic mutations or a variety of other permanent molecular alterations which re-direct "channels" distributing energy dissipation. These are organised along fractal networks (fractal entropy) and are not necessarily structure-dependent. "Oncogenic" alterations of any kind create cumulative effects by permanently stabilising parts of the fractal network, resulting in fractured co-ordination and re-direction of entropy into increased dynamic activity, which is the universal hallmark of cancer. The mechanism of fractal entropy employs Chaos and fractal theories and is illustrated with Mandelbrot figures for fractal distributions and Chaos theory for its influence in creating fractal distributions and their behaviours. The proposal is examined in an *in vitro* heamatopoietic model (IL3 dependent cells) concerning regulation by growth factors of metabolism, apoptosis, oncogenesis and cell dormancy, and suggests new avenues of multi-disciplinary research.