

SPRINGERBRIEFS IN SYSTEMS BIOLOGY

Emily G. Armitage
Helen L. Kotze
Kaye J. Williams

Correlation-based network analysis of cancer metabolism

A new systems
biology approach in
metabolomics



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Contents

1 An Overview of Cancer Metabolism	1
References	4
2 Cancer Hypoxia and the Tumour Microenvironment as Effectors of Cancer Metabolism	7
2.1 Hypoxia-Inducible Factors and Their Role in Tumour Hypoxia	8
2.2 Tumour Hypoxia: The Impact on Treatment	10
2.3 Strategies to Overcome Chemotherapy Resistance in Tumour Hypoxia	11
References	12
3 Metabolic Fingerprinting of <i>In Vitro</i> Cancer Cell Samples	15
References	19
4 Network-Based Correlation Analysis of Metabolic Fingerprinting Data	21
4.1 Calculating Correlation Coefficients	23
4.1.1 Correlation Coefficient Transformation	26
4.1.2 Determining the Significance of a Correlation Coefficient ...	27
4.1.3 Determining the Significance of Difference Between Correlation Coefficients	28
4.2 Network Analysis	30
4.2.1 Currency Metabolites	31
4.3 The Use of Network-Based Correlation Analysis in Reality	32
References	33
5 Case Study: Systems Biology of HIF Metabolism in Cancer	35
5.1 Hypoxia Inducible Factor—1	35
5.2 Network-Based Correlation Analysis of HIF-1 Metabolism	36
5.2.1 Correlation Analysis	38
5.2.2 Network-Based Correlation Analysis	41
5.3 Conclusion	46
References	47

6 Case Study: Systems Biology of Chemotherapy Resistance in Hypoxic Cancer	49
6.1 Doxorubicin	49
6.2 Network-Based Correlation Analysis to Study Hypoxia Induced Chemoresistance	53
6.2.1 Correlation Analysis	54
6.2.2 Network Analysis	56
6.3 Conclusion	59
References	59

Chapter 1

An Overview of Cancer Metabolism

The metabolome is considered the closest entity to the phenotype of a biological system. It displays the changes made at higher hierarchical levels such as the proteome, transcriptome and genome. For many diseases including cancer, studying the metabolome enables us to gain a better understanding of global biological response of cancer cells in the progression of the disease. Revealing the complexity of the metabolome is particularly advantageous to understand the phenotypic function of a cancer cell that is governed by the preceding levels (proteins, transcription factors and genes).

Cancer metabolism has been studied for decades, revealing cancer cell function in order to provide an insight into the disease. Differences in central carbon metabolism between cancerous and normal cells were first demonstrated by Otto Warburg in the 1920s (Warburg et al. 1927). He evaluated the metabolic consumption of glucose and found that cancer cells preferentially used glycolysis over oxidative phosphorylation even in the presence of oxygen (Warburg 1956). This so-called “Warburg effect” is frequently observed in many cancer types, although the underlying basis and consequence of this phenomenon are still not wholly clarified and there appears to be no single mechanism that drives an aerobic tumour cell towards a glycolytic phenotype. Indeed, it is likely that there is plasticity in how a cancer cell metabolises glucose, dependent on glucose availability and the local cellular microenvironment among other potential influencing factors. Furthermore, elevated glucose levels can suppress both glycolysis and oxidative phosphorylation via the “Crabtree effect”, which is generally accepted as a short-term, reversible response to glucose availability (Diaz-Ruiz et al. 2011).

From the perspective of ATP generation alone, a reliance on glycolysis vs. oxidative phosphorylation makes little sense. However, the main hypothesis ventured for why the Warburg effect benefits cancer cells is focused less on ATP generation per se and more on coincidental generation of the cellular building blocks required in rapidly proliferating cells. Glycolysis can provide intermediary precursors that feed into many biosynthetic pathways that ultimately generate nucleotides, amino acids and lipids as well as ATP.

This is achieved by multiple mechanisms. Cancer cells generally upregulate the expression of glucose transporters (predominantly Glut-1), enabling enhanced