John Garland, Metabolomics 2014, 4:2
http://dx.doi.org/10.4172/2153-0769.S1.026

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference and Exhibition on
Metabolomics & Systems Biology
March 24-26, 2014 Hilton San Antonio Airport, San Antonio, USA

The energetics of cancer cells: Challenges for multi-omics

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Cancer is conceived as a de-regulation of networking initiated by a specific mutation or singular "epigenetic" event. However:

It occurs overwhelmingly in homeothermic animals. All cancers share the same and progressive increases in motility, migration, proliferation and internal structural degradation (anaplasticity), regardless of origin. It is extremely rare on a per-cell basis and even high-penetrance, inherited cancer-prone syndromes take years to emerge. Some 200 widely different "oncogenes" and "epigenetic" mechanisms have been identified. These suggest: inducer specificity is low; cancer is coupled to homeothermic metabolism; and induction follows a universal process in which energy usage is progressively focused on activity at the expense of structure-building. 1. Homeotherms generate heat through movement (muscle activity) and mitochondrial uncoupling e.g. by UCP's. How is cancer related to these thermodynamics? 2. The rarity of cancer indicates very low frequency events from singular origins in a lot of background (stochastic resonance over many networks?). 3. Normally, self-organisation and activity run together. In cancer, they run in opposite directions. 4. Although deregulation of many cell cycle checkpoint regulators and nuclear disorder is prevalent, proliferation is still ordered.

This confusing complexity presents real challenges because there are so many inducers with different signaling pathways, and both structure and function change progressively. To determine where any specific observation fits in cancer induction is difficult because unitary origins are rapidly superceded by ever-enlarging dynamic networks. And while cancer cell metabolism is regarded as different ("Warburg effect"), mixed metabolism is expressed by many cells particularly in culture. The link between energy production/usage and the consistent changes in cancer cells is far from clear.

However, a direct link between external thermodynamics and metabolism is illustrated by a well-known model, IL3-dependent cells. They are only created from functional mouse bone marrow cultures generated at 33C which express no IL3; at 37C neither marrow function nor IL3-dependent cells are created, nor do they exist or survive *in vivo*. They depend totally on IL3 receptor signaling and like cancer cells have mixed-phenotype expression. Similarly, they display pure glycolytic metabolism although mitochondria are normal. Without IL3, they immediately apoptose, but if apoptosis is inhibited, they enter reversible metabolic arrest and can undergo reversible structural degradation reminiscent of cancer cells. Thus, a transient, small temperature shift reproducibly creates major cancer-like metabolic and phenotypic changes.

A model for cancer induction has been offered where energy dissipation (entropy) is pivotal, fractally distributed and has origins in chaotic events (Fractal Entropy). This creates a highly dynamic "map" of energy dissipation as represented by Mandelbrot figures in which components, whether for enzymic reactions or assembly/organization, find/optimize permissive entropic environments. FE is dynamically non-linear but seamlessly integrates sequential pathways and elements of different systems in the same space.

In cancer initiation, initiators produce constitutive variants of transient functional activators, replacing chaotic foci with persistent dissipation and inevitably altering fractal distribution. This optimizes entropic environments elsewhere for other functionally-unconnected systems. Since dynamic activities are inherently more dissipative than structure-building, this favours components linked to dynamic activity. The imbalance in entropy distribution between structure and activity progressively widens and the cell increases dynamic activity at the expense of self-organisation. The potential to abnormally create unregulated, and persistent entropic diversion is quite wide, hence the non-specificity of cancer induction. In this model, cancer is a property of altered energy/metabolic management.

These areas will be discussed in more detail, with reference to current studies in metabolite regulation of cancer.If multi-omics, and particularly metabolomics, could become an integral part of all cell and molecular projects/programs in cancer research, its explanatory power may unravel many complexities and enable creation of designer therapies – cancer's ultimate goal.

Biography

Dr. Garland is a graduate in Medicine, Microbiology and Molecular Biology from Edinburgh University. The work on IL3 was performed with Mike Dexter in the Paterson laboratories, Manchester; the University of Manchester; and with Andrew Halestrap in Bristol University.

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