Reverting to Single Cell Biology in Cancer

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What is cancer as a biological phenomenon?

Why does it exist?

What is its place in the great story of life on Earth?
Cancer is a window on the past
Cancer across the tree of life

C. Athena Aktipis et al. Phil. Trans. R. Soc. B
2015;370:20140219
Key fact: cancer pervades multicellular life

Cancer is not “life gone wrong” but a deep-rooted and therefore ancient property of life itself. To understand cancer we need to know its place in the overall story of life.
Fasciations in plants

C. Athena Aktipis et al. Phil. Trans. R. Soc. B
2015;370:20140219
Cancer in hydra

C. Athena Aktipis et al. Phil. Trans. R. Soc. B
2015;370:20140219
Origin of cancer: tracing its deep evolutionary roots

"Nothing in biology makes sense except in the light of evolution."

Theodosius Dobzhansky

Cancer is the re-expression of an ancestral phenotype (atavism)
Basic hypothesis

In cancer, cells re-wire information flows to default back to ancestral unicellular pathways and ancestral phenotypes.
Theodor Boveri (1914)

“I regard it as beyond doubt that the tendency to multiply indefinitely is a primaeval property of cells.”

If regulatory mechanisms are disrupted:

“...this change may well be enough to induce an altruistic cell to revert to its egoistical mode and thus release its multiplication from restraint.”
Cancer is a breakdown of the ancient cooperative contract between cells and organism
The five foundations of multicellularity

Cancer: the “cheating phenotype”
Some predictions

• Gene *ages* will be a key factor in cancer incidence and progression.

• Cancer should show a transcriptional shift toward unicellularity.

• The cancer phenotype should be suppressed when a tumor is placed in a physiologically normal multicellular environment. The immediate microenvironment of a malignant tumor is not actually physiologically normal.
A phylostratigraphy approach to uncover the genomic history of major adaptations in metazoan lineages

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Macroevolutionary trends traditionally are studied by fossil analysis, comparative morphology or evo-devo approaches. With the availability of genome sequences and associated data from an increasing diversity of taxa, it is now possible to add an additional level of analysis: genomic phylostratigraphy. As an example of this approach, we use a phylogenetic framework and embryo expression data from Drosophila to show that grouping genes by their phylogenetic origin can uncover footprints of important adaptive events in evolution.

Introduction

Comparison of metazoan genome sequences has shown that a significant fraction of genes occurs only in defined lineages [1–8]. This implies that these genes have arisen during the evolution of the respective lineages, probably in the context of lineage specific adaptations (see Glossary). The origin of such new genes seems to occur in a punctuated manner, that is, new genes initially evolve very quickly until they become locked into a pathway [2–4]. If these genes would then retain an association with a particular pathway, one could infer their evolutionary origin on the basis of the function of the genes in extant organisms and of an assessment of their phylogenetic emergence (see Introduction in Online Supplementary Material). This is the principle of “phylostratigraphy”, which we present here as a general approach to trace evolutionary innovations using data from genome projects.

The best data for a pan-metazoan statistical evaluation of gene evolution are currently available from Drosophila and we have focused our analysis on this dataset. However,
Phylostratigraphic tracking of cancer genes suggests a link to the emergence of multicellularity in metazoa

Tomislav Domazet-Lošo and Diethard Tautz

Abstract

Background: Phylostratigraphy is a method used to correlate the evolutionary origin of founder genes (that is, functional founder protein domains) of gene families with particular macroevolutionary transitions. It is based on a model of genome evolution that suggests that the origin of complex phenotypic innovations will be accompanied by the emergence of such founder genes, the descendants of which can still be traced in extant organisms. The origin of multicellularity can be considered to be a macroevolutionary transition, for which new gene functions would have been required. Cancer should be tightly connected to multicellular life since it can be viewed as a malfunction of interaction between cells in a multicellular organism. A phylostratigraphic tracking of the origin of cancer genes should, therefore, also provide insights into the origin of multicellularity.
We find two strong peaks of the emergence of cancer related protein domains, one at the time of the origin of the first cell and the other around the time of the evolution of the multicellular metazoan organisms.
Altered interactions between unicellular and multicellular genes drive hallmarks of transformation in a diverse range of solid tumors

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Tumors of distinct tissues of origin and genetic backgrounds exhibit a common hallmark cellular phenotypes, including invasive growth, evasion of apoptosis, angiogenesis, and metastasis. The evolution of multicellularity in the context of tumor initiation and progression is described.

Keywords: evolution; systems biology; networks; atavism; multicellularity; network medicine

How the evolution of multicellularity set the stage for cancer

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Altogether 40% of human genes are assigned to unicellular ancestors (phylostrata 1-3), and 60% were assigned to multicellular ancestors (phylostrata 4-16).
Compared to normal, cancer increases the proportion of its transcriptome coming from unicellular genes.
Trigos et al, PNAS 2017
Less differentiated tissues have older transcriptomes
Further predictions

• Younger genes should be enriched in mutations in cancer
• Genes that are causally involved in cancer should be older than the emergence of complex multicellularity 600 million years ago.
• Cancer should employ unicellular responses to cellular and environmental stresses.
Ancient genes establish stress-induced mutation as a hallmark of cancer

Luis Cisneros¹,²*, Kimberly J. Bussey¹,³*, Adam J. Orr⁴, Milica Mićević⁵, Charles H. Lineweaver⁶, Paul Davies²

[Bar chart showing frequency of mutations over millions of years.]
• Genes causally implicated in cancer are under-represented among young (<500 MY) genes.
• Dominant COMSIC genes are younger than recessive COSMIC genes
Functional enrichment network of recessive COSMIC cancer genes highlights DNA repair and cell cycle control.
DOES EVOLUTION EVOLVE UNDER PRESSURE?

Stage III Sacroccocygeal endodermal sinus tumor

48-51,XY,add(1)(p36),+add(2)(q31),
+3,+3,add(6)(q27), add(10)(q26),
add(15)(p11),+mar1,+mar2[cp7]/
46, XY[13]

Adapted from Figure 2, Bussey et al, Cancer Genet Cytogenet
25:134-46, 1999
Regulation of the error-prone DNA polymerase Polk by oncogenic signaling and its contribution to drug resistance

Kelsey Temple1,2,*, Nathan R. Campbell1,2,*, Richard Huang3, Erin M. Langdon3,4, Theresa Simon-Vermot1,4
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MTOR signaling orchestrates stress-induced mutagenesis, facilitating adaptive evolution in cancer

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Adaptive mutability of colorectal cancers in response to targeted therapies

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SItH (Stress Introduced Heterogeneity) Score

The SItH Score is a way of quantifying how mutations are distributed in a cluster.
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<thead>
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<th></th>
<th>Cox Proportional Hazard Regression</th>
<th></th>
<th>Observation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grouping</td>
<td>HR</td>
<td>CI</td>
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<tr>
<td>Overall SltH</td>
<td>Primary Tumors</td>
<td>0.4184</td>
<td>0.1983 - 0.8829</td>
</tr>
<tr>
<td></td>
<td>Recurrent and Metastatic Tumors</td>
<td>7.987</td>
<td>1.241 - 51.41</td>
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<tr>
<td>Cluster SltH IQR</td>
<td>N/A</td>
<td>5.045</td>
<td>1.399 – 18.19</td>
</tr>
<tr>
<td></td>
<td>IQR above or below median</td>
<td>1.37</td>
<td>1.1011 - 1.705</td>
</tr>
</tbody>
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CI: Confidence Interval
Therapeutic Implications

• Single cells EVOLVE to survive. If cancer is single cell behavior, then adaptability is a selectable trait.

• “Take no prisoners” will apply a strong selective pressure that will select for adaptability and thus resistance.

• To take advantage of adaptability, we should think about what multicellularity “buys” a cell and create therapies that select for those behaviors rather than selecting against unicellular behavior.

• Need a way to characterize tumors that takes into account both adaptive potential of the tumor and the host’s available cancer defenses.
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David Goode
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Pan-Cancer Analysis Working Group (PCAWG)
1000 Genomes Project
Clustering versus mutational load
Selection increases structural but not numerical abnormalities
The stroma as a crucial target in rat mammary gland carcinogenesis

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Stromal Regulation of Neoplastic Development

Age-Dependent Normalization of Neoplastic Mammary Cells by Mammary Stroma

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American Journal of Pathology, Vol. 167, No. 5, November 2005
Transmembrane potential of GlyCl-expressing instructor cells induces a neoplastic-like conversion of melanocytes via a serotonergic pathway

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