The Giant Cells: Toward Unification of Embryogenesis, Cancer, and Evolution

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We have not made much progress in the past 50 years won’t advance much more in another 50 if we insist on the same-old same-old, all of us in the biomedical research need to descent from our high horse and humbly admit where we have been wrong” ..... 

“Cancer is not linear--it is completely non-linear. It lives in the science of chaos”!
We lack the conceptual paradigms and computational strategies for dealing with this complexity.
What has been wrong?
What could be right?
How to move forward?
Fundamental question in life and cancer?

- What is human life?
- What is cancer?
- Is cancer a life or a cluster of mutated cell?
19th century scientist

I must find the explanation for this phenomenon in order to truly understand Nature...

Curiosity driven, Darwinian approach

21st century scientist

I must get the result that fits my narrative so I can get my paper into Nature...

Molecular driven-Mechanism
Cancer is Defined by Microscopic Criteria by Pathologists
Nothing is more important to the individual with a tumor than being told “it is benign”
Differences Between Benign and Malignant Tumors

- **Level of Differentiation** (Tissue immaturity)
- **Nuclear grade** (Nuclear atypia, size variation, and tumor giant cells)
Any viable theory of cancer must be able to explain the benign and malignant phenotypes observed by pathologists

- *Tumor size* has nothing to with malignancy – measurement of tumor size as endpoint will fail the patients
Polyploid Giant Cancer Cells (PGCCs) Can Grow back
(Hey Ovarian Cancer Cell Line, 09/22/2010)

450 μM CoCl₂

1 Month Later
Dogma

Polyplloid giant cancer cells (PGCCs) are believed to be non-dividing and degenerating cells (trash cells, >100 years)
The Human Life Cycle

Senescence/Degeneration

Cancer

- fertilised egg
- foetus
- baby
- child
- adolescent
- old age
- adult
- death
Life Starts with a Giant Cell
(largest human cell)

- Nucleus: 160 μM (Normal cells 10-12 μm)
- Zona Pellucida: 4,000,000 μm³ vs 3,000 μm³
  (Hela cell)
Pre-Embryonic Period (Weeks 1-2)

Differentiation

Dedifferentiation

32 cells

Differentiation

page 64, figure 3.5
Life Code (Cleavage)

\[ 2^5 = 32 \]

2, 4, 8, 16, 32
Embryonic Chaos in Human

Lack of Cell Cycle Checkpoint
Mosaicism
Atypical Cell Division
Cellular Fragmentation
Sub-chromosomal instability
Micro-nucleation
Chromothripsis

Daughtry and Chavez, 2016
Chaos in Early Human Embryo

“It's amazing that any of us has made it this far, let alone that and of our children are healthy”.


Chromosome instability is common in human cleavage-stage embryos. Vanneste et al., Nature Medicine 15 (577-583), 2009
Chaos Theory: Extremely sensitive to initial stimulus: Non-linear mechanism to create a new order from a disorder.
Tumors are a spectrum of diseases along development (Barry Pierce)

- Uterus
- Embryonic development
- Ovary/Testis
- Parthenogenesis
Dev-Arrested Tumors: First Cancer Cell(s) are defined by amount of embryonic tissue (Quantity)
Bilaminar disk stage: Polyembryoma
Gastrulation stage: Immature teratoma

Organ developmental stage: Wilms tumor
Somatic-derived first cancer cells are defined by nuclear grade (quality)

Atypia, increased N/C ratio, pleomorphism, PGCCs

- Quality of Cells: Born to be bad
#1. Could the initiation of high grade cancer go through a reproductive process similar to that of human embryo?

#2. Could be the giant cell a somatic equivalent of an “egg”?
Unexpected finding #1: Primitive cell division
Human Embryonic Stem Cells

PGCCs
Budding from Binucleated PGCC (amitosis)
Unexpected finding #2:
A tissue morphology code
Big Bang Division of a Giant Cell: The Origin of Tissue
Zhang et al,
IJ Cancer, 2013
Zhang S. et al, 2013, Cancer Lett
Unexpected finding #3: A mechanism to generate germ tumors
Blastocyst-like

Disfigured blastocyst
Morula-like Multinucleated PGCC
Unexpected finding #4

Mechanism of whole genomic reorganization: Genomic Chaos (Henry Heng)
The Giant Cell Life Cycle

Phase 1: Initiation
2n, 2c → pn, pc (≥ 4n, 4c)

Phase 2: Self-renewal
pn, pc (≥ 4n, 4c)

Phase 3: Termination
pn, pc (≥ 4n, 4c) → 2n, 2c

Phase 4: Stabileness
2n, 2c

Mitosis
Amitosis: no spindle/no nuclear membrane breakdown
Blastomere Growth and Division: Hardy, 1993, J reproduction and Fertility (McClintock)
Giant Ovum Pathway

Egg (+/- sperm) → Cleavage (Chaos) → Dedifferentiation → Differentiation/Arrest (embryonic tissue)
Senescent Giant Cell Pathway

Aging somatic cells

Endoreplication (Chaos)

Dedifferentiation

Arrest (undiff tumors)
The Origin of Species: “Polyploidy allows quick whole genomic reorganization in response to environmental stress and allows a punctuated macro-evolution for new species”
First Cell in Life: The Giant Cells
ORIGINAL ARTICLE
Generation of cancer stem-like cells through the formation of polyploid giant cancer cells
S Zhang\textsuperscript{1,2}, I Mercado-Uribe\textsuperscript{1}, Z Xing\textsuperscript{1}, B Sun\textsuperscript{3}, J Kuang\textsuperscript{4} and J Liu\textsuperscript{1}

ORIGINAL ARTICLE
Linking genomic reorganization to tumor initiation via the giant cell cycle
N Niu\textsuperscript{1}, J Zhang\textsuperscript{1}, N Zhang\textsuperscript{1}, I Mercado-Uribe\textsuperscript{1}, F Tao\textsuperscript{1}, Z Han\textsuperscript{2}, S Pathak\textsuperscript{3}, AS Multani\textsuperscript{3}, J Kuang\textsuperscript{4}, J Yao\textsuperscript{2}, RC Bast\textsuperscript{4}, AK Sood\textsuperscript{5}, M-C Hung\textsuperscript{2,6} and J Liu\textsuperscript{1,2}

ORIGINAL ARTICLE
Dedifferentiation into blastomere-like cancer stem cells via formation of polyploid giant cancer cells
N Niu, I Mercado-Uribe and J Liu
The dualistic origin of human tumors

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Review

The “life code”: A theory that unifies the human life cycle and the origin of human tumors

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