Real world in cancer? Epistemology of the origin of cancer: new paradigm for the majority of cancers

Background: The somatic mutation theory as the origin of cancer (carcinogenesis) was born some 100 years ago, when Theodor Boveri 1914 suggested that a combination of chromosomal defects may result in cancer. This was followed by Karl-Heinrich Bauer in 1928 suggesting that mutations could cause cancer. Subsequently, in 1953 Carl Nordling proposed that a number of mutated genes could cause cancer. Alfred Knudson in 1971 proposed that one hit (one mutation) would result in a clone of cancerous cells. This was modified to a 2-hit-theory later and it seems that cancer biology has continued to try to bolster the somatic mutation theory by recently suggesting that ‘driver’ and ‘passenger’ mutations were necessary and when this proved insufficient, others proposed the hyper-mutation theory in 2014. In the attempt to clothe the Emperor, it was forgotten that mutations found in advanced cancers are either late events or epiphenomena that occur after carcinogenesis (cancer development) and especially after the appearance of a precancerous niche. Reality: Fewer than 10% of cancers are proven to be hereditary (i.e., causally related to germline mutations) and this ratio is even lower in cancers of the stomach (<1%), the colorectum (3-8%) and breast (8%). Infection-triggered cancers constitute some 15% of all cancers and the remaining about some 80% cancers are sporadic, meaning their cause is unknown. New cancer paradigm: Findings from the plant and animal kingdoms, molecular and clinical data over the last 250 years were critically reviewed and gave rise to a new cancer hypothesis containing a multi-step process of 6 sequences. These include, (1) a pathogenic biological or chemical stimulus is followed by (2) chronic inflammation, from which develops (3) fibrosis with associated changes in the cellular microenvironment. These remodeling changes result in a (4) precancerous niche, which triggers the deployment of (5) a chronic stress escape strategy, and when this fails to resolve, (6) a transition of a normal cell to a cancer cell occurs.
**Consequences:** This recently proposed cancer model explains the origins of the vast majority of cancers which are until now were referred to as ‘sporadic’ cancers. Furthermore, this theory points out the need to establish preventive measures long before a cancer becomes clinically apparent. The epistemology of the origin of cancer is reviewed and presented.
REAL WORLD IN CANCER?

Epistemology of the Origin of Cancer

new paradigm for the majority of cancers

Björn Brücher and Ijaz Jamall

6th March 2015, Munich, Germany
disclosures

nothing
epidemiology and health care
Age distribution and CANCER

age distribution and incidence in cancer

Anzahl pro 100.000 Personen

males

gender distribution in cancer

females
common diseases in the future

**prognosis for 2005 until 2020**
(Mecklenburg-Vorpommern)

- heart attack + 28.5%
- diabetes mellitus + 21.1%
- colon carcinoma + 30.1%
- dementia + 91.1%
Diabetes Growth Projections 2012-2030

Diabetes worldwide drug market size $35 billion
Expected to grow to $58 billion by 2018

Consequences are...

....an enormous challenge....
future goals are
Future goals

- neuro
- onco
- cardio-vascular

goals
- clinical health care & economics
- research & science

cause-based (identify causes) not symptom-orientated

personalized & individualized

translational (the bridge)
some demand.....
future comprehensive molecular profiling
<table>
<thead>
<tr>
<th>Author-year</th>
<th>Method</th>
<th>Trial</th>
<th>Histology</th>
<th>No.</th>
<th>Sample size</th>
<th>Preservation</th>
<th>Time</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Resp</th>
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<td>FFPE</td>
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<td>GAC, ESCC</td>
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<td>RPMI-1640</td>
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<td>Wu, 2012</td>
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<td>s.r.</td>
<td>n.r.</td>
<td>n.s.</td>
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</table>

**No standardization of:**
- Preservation
- Storage of samples
- Use of methods
- Which histology for which methodology
- Follow-up
- Variables to include

*but should be already standard?*
Cancer diagnosis & therapy in the future needs being outcome orientated
proposed anticancer strategy

Personalized Therapy

- Personalized Strategy
  - (by Cancer Classification)
  - Tumor Staging
    - histopathological profile
    - molecular profile
    - metabolic profile
    - immunologic profile
    - response prediction profile
  - Patient Staging
    - calculable risk
    - life quality
    - psychosomatic profile

+ Individualized Therapy

- Individualized Strategy
  - (by Response Evaluation)
  - Tumor Response
    - basic laboratory response profile
    - histopathological response
    - imaging response profile
    - biochemical response profile
  - Patient Response
    - life quality response
    - psychosomatic response profile

Response Classification

stratification

therapy A + therapy B

modification
what is cancer
Cancer is a group of more than 100 diseases that involve the uncontrolled division of the body’s cells.
molecular discoveries

…understand the past,

to judge the present

if you want to change the future.
a combination of chromosomal defects may result into cancer.

1888
he coined the name ‘centrosome’

1914

Theodor Boveri

(* 12.10.1862 - † 15.10.1915)

Bamberg - Würzburg

Karl Heinrich Bauer

(* 26.09.1890 - † 07.07.1978)

Breslau (1933-1943) and Heidelberg (1943-1962)

1928

suggested mutations for the origin of cancer

Bauer KH: Mutationstheorie der Geschwulst-Entstehung. Berlin: Julius Springer Verlag 1928
Erwin Chargaff - 1940 - “Chargaff’s rule”
(11th Aug 1905-20th Jun 2002)

- Four bases may occur in varying proportions in DNA of different organisms

  # of A = # of T
  (w/ two hydrogen bonds)

  # of G and C are present
  (w/ 3 hydrogen bonds)
Martha Chase and Alfred Hershey
(11th Aug 1905-20th Jun 2002)

- radioactive isotope tracer experiment

- bacterial virus (bacteriophage T2) infects a host cell (bacterium Escherichia coli)

- found that T2 virus DNA, not its protein coat, enters the host cell

- genetic information for replication of the virus
Rosalind Franklin and Maurice Wilkins

X-ray diffraction study concluded DNA fibers have two strands.


intellectual debate

and worked on problem of making a DNA molecule model that was double stranded but also had the specific A - T and G - C base equivalencies

Solution: double helical structure for DNA

a number of mutated genes cause cancerous cells

1953

Carl O. Norlding

(* 6th 02.1931 – 15th 02.2007)
Finnland

1962

20th Oct 1962

Nobel Prize in Physiology and Medicine

Francis Crick
James Watson
Maurice Wilkins

not- .........................Rosalind Franklin (she died earlier)
1971

Alfred G. Knudson

(* 9th 08.1922 –)

Los Angeles

1-hit-theory of carcinogenesis

'Knudson hypothesis'

a cell can initiate a tumor only if it contains 2 mutant alleles

a person who inherits a mutant allele must experience a second somatic mutation to initiate carcinogenesis

for the majority of cancer: this is a non-proven theory

Later: 2-hit-theory – it takes two to Tango

Knudson AG: Mutation anc cancer: statistical study of retinoblastoma.
another theory (carcinogen initiate carcinogenesis)

Peter Duesberg
(* 2th 12.1936)
[born in Münster, Germany]
[USA]
carcinogens initiate carcinogenesis with a random aneuploidy

• did isolate the first oncogene
• does not believe in HIV virus

Aneuploid cells are error prone

• as chromosome segregation and maintenance systems

• are disbalanced as a result of unbalancing of spindle proteins, repair enzymes, and centrosome numbers.
Even with an unstable genome, it takes time to accumulate the multiple mutations that are required for cancerous transformation, so cancer is much more common in older people than in young.
since an opinion changed to the… dogma

mutation is „the“ cause for the majority of cancers
mutation theory work for some 5% of cancers

let’s create it a bit differently – may this fits in (2007)

1-concept of ‘drivers‘ and ‘passengers‘

Patterns of somatic mutation in human cancer genomes

Christopher Greenman1, Philip Stephens1, Raffaella Smith1, Gillian L. Dalgliesh1,Christopher Hunter1, Graham Bignell1, Helen Davies1, Jon Teague1, Adam Butler1, Claire Stevens1, Sarah Edkins1, Sarah O’Meara1, Imre Vastrik2, Esther E. Schmidt2, Tim Avis1, Syd Bar thorpe1, Gurpreet Bhamra1, Gemma Buck1, Bhudip Choudhury1, Jody Clements1, Jennifer Cole1, Ed Dicks1, Simon Forbes1, Kris Gray1, Kelly Halliday1, Rachel Harrison1, Katy Hills1, Jon Hinton1, Andy Jenkinson1, David Jones1, Andy Menzies1, Tatiana Mironenko1, Janet Perry1, Keiran Raine1, Dave Richardson1, Rebecca Shepherd1, Alexander Small1, Calli Tofts1, Jennifer Varian1, Tony Webb1, Sofie West1, Sara Widaa1, Andy Yates1, Daniel P. Cahill1, David N. Louis1, Peter Goldstraw4, Andrew G. Nicholson4, Francis Brasseur1, Leendert Looijenga1, Barbara L. Weber7, Yoke-Eng Chiew3, Anna deFazio9, Mel F. Greaves9, Anthony R. Green10, Peter Campbell1, Ewan Birney2, Douglas F. Easton11, Georgia Chenevix-Trench12, Min-Han Tan13, Sok Kean Khoo13, Bin Tean Teh13, Siu Tsan Yuen13, Suet Yi Leung14, Richard Wooster1, P. Andrew Futreal1, and Michael R. Stratton1,9

or another way could be ............
mutation theory work for some 5% of cancers

..creating it even more different….. (2014) – maybe this fits in

2-concept of 'hypermutation theory'

Hypermutation in human cancer genomes: footprints and mechanisms

Steven A. Roberts and Dmitry A. Gordenin*
or maybe we should create in the future the....

(2030?)

ultra-hyper-super-mutation-theory

or maybe we just re-think......
one would expect.......... 

scientists rest, ....pause and re-think

instead trying fitting in (or better: pressing in) a theory, which did work for a minority but not for a majority of cancers.

didn't we have that behavior with cholesterol, salt dietary intake and hypertonus, the climatic change, etc.?
An apple found in a car..............

is **not** synonym of prove apples grow in car‘s.

a correct observation (mutation in advanced cancers) is not synonym of prove being the cause for carcinogenesis (= cancer development)

– **misleadings in science: observation versus wrong conclusion**
frequency of mutations by disease state
mutations status of selected tumors

Colorectal (N = 74)

- KRAS, 64%
- PIK3CA, 18%
- NRAS, 4%
- PIK3R1, 3%
- RUNX1, 3%
- SMO, 3%
- RET, 1%
- No mutation detected, 24%
- ABL1, 1%
- BRAF, 4%
- CTNNB1, 1%
- IDH1, 1%
- GNAS, 1%
- GNA11, 1%
- ERBB2, 1%

Lung (N = 85)

- KRAS, 20%
- EGFR, 15%
- KIT, 1%
- BRAF, 1%
- STK11, 7%
- SMO, 1%
- WT1, 1%
- RUNX1, 5%
- PIK3CA, 1%
- MET, 5%
- MAP2K1, 2%
- No mutation detected, 55%
but it also seems being different where....

colorectal cancer incidence map USA (2009)
mutations and genetics are.....

of significant importance,

for understanding biology

or even (partially) nature

but don’t explain anything!
reality (1): cancer is triggered in

- 5-10% hereditary
- 15% inflammation
- 80% sporadic (=unknown!!)
gastric carcinoma
Reality (2)

DNA alterations are not the sole criterion for phenotypical changes
genes and important numbers

- how do polymorphisms reflect a disease?
- number of SNPs: 62,676,337 (23 Jul 2013)
- humans have 23 paired chromosomes (46)
- with 21,000 haploid coding genes
- and appr. $3.3 \times 10^9$ base pairs
- chromosome 1 with 249,250,621 base pairs has 4,401,091 variations
- $10^{-6}$ to $10^{-10}$ in eukaryotes
and

- number of pseudogenes is: 13,000

- e.g. Alu has 50,000 active copies

- appr. more than 40% of the total genome

- e.g. mitochondrial genome

- non-coding DNA is about 98% of the human genome

- maybe - someday - big data
real world?
.....if you have a smoky engine........
you may take the car to....
detecting particles in the smoke....
....making nice pictures and to....
..measure particles in the smoke for making the diagnosis
basal membrane and extracellular matrix

Strength – Triple helix provides tensile strength

Scaffold – Provides organization and structure for the ECM

Without it, what would happen?

- Loss of cell-cell communication
- Cell migration
- Loss of cell shape

Epistemology of the origin of cancer: a new paradigm

1. Pathogenic stimulus
   - Acute Inflammation

2. Chronic Inflammation
   - Cytokines (IL6, IL8, GM-CSF)
   - Apoptosis
   - TGFβ
   - Fibroblasts
   - LOX (cross-linking collagen)
   - Re-modeling ECM (cross-linking collagen)

3. Fibrosis
   - Cross-linking collagen

4. Pre-cancerous niche
   - Remodeling ECM

5. CSES
   - Chronic-Stress-Escape-Strategy
   - Normal Cell
   - Malignant Cells

6. NCCCT
   - Normal-Cell-Cancer-Cell-Transition

Later Events
   - Mutagenesis / Genomic Instability
   - Proliferation & Angiogenesis
   - Detachment / Invasion
   - Metastasis

Join the web group

<table>
<thead>
<tr>
<th>NEW MEMBERS</th>
<th>MEMBERS</th>
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<tbody>
<tr>
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<td>1,957</td>
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Like any community, a LinkedIn group might be close-knit or vast, brand new or already thriving. Explore this group to see if it's right for you.

<table>
<thead>
<tr>
<th>TOTAL MEMBERS</th>
<th>NEW MEMBERS LAST WEEK</th>
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Thank you very much for your kind attention!