The value of pathology: on genes, memes and quality

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The beginning
Life

The Evolution of Humans from Single Cells to Today

All cells are eukaryotic:
- Archea
- Bacteria
- Protists
- Fungi
- Plants
- Animals

Pre-cellular life
- RNA
- Protein synthesis
- Self-replicating elements
- First cells

Prokaryotes
- 3,500,000,000 years (ybp)
- Simple single-celled life

Eukaryotes
- 2,000,000,000 ybp
- Cells with nuclei

Chromatophores
- 900,000,000 ybp
- Multicellular, differentiated tissues

Cnidarians
- 580,000,000 ybp
- The ability to move and eyes

Flatworms
- 550,000,000 ybp
- Bilateral symmetry & brain

Worms, Moluscs, Crustaceans, Insects

Arthropods

 Cambrian Explosion
- 540,000,000 ybp
- Insects, arachnids, spiders, scorpions

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- Rapid emergence of most major fossil groups

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K-T Extinction
- 65,000,000 ybp
- Dinosaurs
- Extinction of non-avian dinosaurs

Proto-Polypetes
- 550,000,000 ybp
- Tree-dwelling

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Dinosaurs
- 220,000,000 ybp
- Mammals
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Age of Reptiles
- 240,000,000 ybp
- Non-avian dinosaurs

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Age of Mammals
- 100,000,000 ybp
- Smaller brains
- Proportionally smaller jaws
- Body hair
- New world monkeys
- Old world monkeys
- Gibbons

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Homo Erectus
- 1,700,000 ybp
- The ability to control fire and discerned body hair

Homo Sapiens
- 200,000 ybp
- Advanced tool use

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Neanderthals

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Genetic and cultural evolution in a glance
Cultural evolution

Cultural history

The demands of complex technology may have pushed human culture to accelerate, though it seems to have evolved not steadily but in leaps and bounds.

2.5 million years ago
Oldest stone tools

400,000 years ago
Earliest strong evidence of cooking dates from this period

120,000 years ago
Early signs of pigment use suggest the emergence of symbolic culture at this time

50,000 years ago
The "cultural revolution", including ritualistic burials, clothes-making and complicated hunting techniques

10,000 years ago
Agriculture begins

4500 years ago
Great Pyramid at Giza built

2.5 million years ago

1.6 million years ago
Tools begin to become more complex, including skilfully shaped, symmetrical hand-axes

160,000 years ago
Early humans begin to use fire to treat stone tools

100,000 years ago
Shell beads give the earliest evidence of jewellery

35,000 years ago
An explosion of cave art in Europe. First surviving statue of a woman

5000 years ago
Oldest known writing

420 years ago
Shakespeare’s plays first performed in London
The classic evolution theory of cancer
Genetic evolution as a meme
Heterogeneity from the beginning
The cancer stem cell

- A long living cell that acquires at least 6-8 genetic alterations in different categories of processes
- Little turnover
- Hidden
- Hard to find
- Hard to hit
Hanahah and Weinberg, Cell 2000 Hallmarks of Cancer

- Sustaining proliferative signaling
- Resisting cell death
- Inducing angiogenesis
- Enabling replicative immortality
- Evading growth suppressors
- Activating invasion and metastasis
But how to hit the cancer stem cell?
Origin of the Meme

- Oxford zoologist Richard Dawkins is credited with the first publication of the concept of meme in his 1976 book *The Selfish Gene.*
Similarities and differences between cultural and genetic evolution
Genes & memes - genetic vs cultural adaptation

**Genes**
- Determine individual anatomical, physiological and neurological capacities
- Mutation: physical change to one or more DNA nucleotides on a chromosome
  - Change is slow *multi-generational* process depending on natural selection
  - Movement rather than increased versatility

**Meme** = unit of culture (an idea or value or pattern of behavior or knowledge) that may be passed between individuals or from one generation to another by non-genetic means
- Change *often intra-generational* depending on innovation, social relationships and processes
- Transmission limited by genetic capacity to communicate detailed information
- Essential information easily lost or corrupted over generations.
- Rate and extent of cultural accumulation depend on genetic capacity, group size, (culturally transmitted) cultural practices
Survival of the fittest

- Not survival of the best or the strongest
- Ideas that fit are not always the best or the strongest
- Science is not a democracy, nevertheless, ideas must fit
Memes and timing

- Nagtegaal ID, Marijnen CA, Kranenbarg EK, Mulder-Stapel A, Hermans J, van deVelde CJ, van Krieken JH. Local and distant recurrences in rectal cancer patients are predicted by the nonspecific immune response; specific immune response has only a systemic effect--a histopathological and immunohistochemical study. BMC Cancer. 2001;1:7.


Dubious memes in pathology

- Invasive growth precedes metastasis
- Cancer in situ
- Low grade lymphomas are malignant
- Modern classifications are almost perfect
- The correct diagnosis exists
- *Etc. please send me more!!!!*
Words are the strongest memes: Organoids

Quality: various memes???
Quality of pathology

Quality by pathologists

• Nagtegaal ID, van Krieken JH. The role of pathologists in the quality control of diagnosis and treatment of rectal cancer - an overview. Eur J Cancer. 2002
• van Krieken JH, Nagtegaal ID. Pathological quality assurance in gastro-intestinal cancer. Eur J Surg Oncol. 2005
• Mekenkamp LJ, van Krieken JH, Marijnens CA, van de Velde CJ, Nagtegaal ID; Pathology Review Committee and the Co-operative Clinical Investigators. Lymphnode retrieval in rectal cancer is dependent on many factors--the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. Am J Surg Pathol. 2009
Quality in clonality testing

• Hoeve MA, Krol AD, Philippo K, Derksen PW, Veenendaal RA, Schuuring E, Kluin PM, van Krieken JH. Limitations of clonality analysis of B cell proliferations using CDR3 polymerase chain reaction. Mol Pathol. 2000


• van Krieken JH et al. Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia. 2007
Quality in molecular pathology (1)


Quality in molecular pathology (2)

Quality in molecular pathology (3)


• Tack V, Ligtenberg MJL, Siebers AG, Rombout PDM, Dabir PD, Weren RDA, van Krieken JHJM, Dequeker EMC. RAS testing for colorectal cancer patients is reliable in European laboratories that pass external quality assessment. VirchowsArch. 2018
Quality in immunohistochemistry

Quality by teams

Quality in data

- Nagtegaal ID, Kranenbarg EK, Hermans J, van de Velde CJ, van Krieken JH. Pathology data in the central databases of multicenter randomized trials need to be based on pathology reports and controlled by trained quality managers. J Clin Oncol. 2000

External quality assessment more important than ever

- The result of a single test determines clinical management
- Processes/Technology more complicated
- Rapid changes in scope
IQNpath: An international network for quality in tissue-based pathology

Mission
• International multi-stakeholder expert group focused on improving quality of clinical biomarker testing in pathology

Organisation
• Non-profit association (network)
• EQA provider members
• Corporate sponsors (membership fee & specific project funding)

Activities
• Publications, guidelines & training: Advocate EQA/PT & education
• Multi-stakeholder Communication: Working Groups, Workshops
• Best practice for EQA: Scheme badging
• Verification/endorsement: Badging standards, controls, tools
• EQA and other data collection: Database

www.iqnpath.org
Conclusions

- Cancer is a side effect of evolution
- Cancer stem cells are the holy grail
- Memes are strong determinants of our thinking
- The origin of memes is often difficult to find
- Challenging memes is the start of new insights