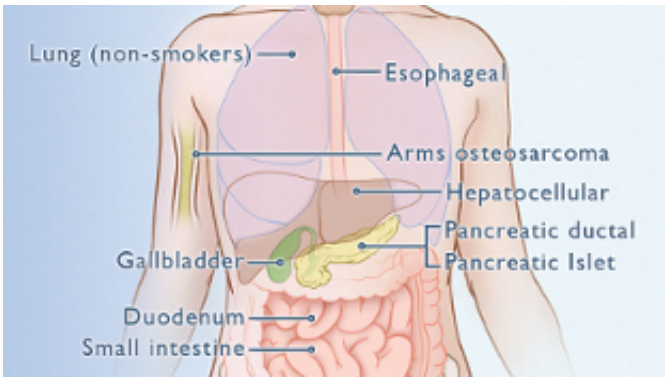
Stem Cell Divisions Help Explain Cancer Risk

An analysis of 31 tissues finds that random mutations acquired during stem cell divisions correlate with lifetime cancer risk—more so than heritable mutations and environmental factors combined.

By Anna Azvolinsky | January 1, 2015



C. TOMASETTI, B. VOGELSTEIN AND ILLUSTRATOR ELIZABETH COOK, JOHNS HOPKINS UNIVERSITY

While genetic and lifestyle factors can influence whether a person develops cancer, according to a study published in *Science* today (January 1), random chance also appears to play a major role.

Cancer rates among adult tissues vary substantially. For example, a person's risk of getting lung cancer is more than 11 times that of developing brain cancer—and eight times greater than that of stomach cancer. Researchers have attributed these differences in cancer rates to environmental risk factors, such as smoking or exposure to ultraviolet light, as well as to heritable mutations. But neither environmental factors nor inherited genetic variation can fully explain the substantial variability in cancer rates across tissues. Moreover, the total numbers of cells that make up these tissues also cannot explain varying cancer risk.

Researchers at Johns Hopkins University have now found a third factor that helps explain these differences: the number of lifetime stem cell divisions. Using available data on the number of stem cells and their rates of division in 31 different tissues, Cristian Tomasetti, a mathematician who studies oncology at the Johns Hopkins University School of Medicine and Bert Vogelstein, a cancer geneticist at the Johns Hopkins' Sidney Kimmel Cancer Center in Baltimore, found that about 65 percent of the variation in cancer risk among tissue types can be explained by the number of stem cell divisions a tissue undergoes within its lifetime. The greater the cumulative number of stem cell divisions, the higher the cancer rate in that tissue.

Plotting lifetime cancer risk versus the total number of stem cell divisions left little doubt about this strong relationship, which applied even for cancers with 100,000-fold differences in lifetime risk, Vogelstein told *The Scientist*.

"The message is straightforward and clear," said Giovanni Parmigiani a statistician and chair of the department of biostatistics and computational biology at the Dana-Farber Cancer Institute in Boston, who was not involved in this study but has previously collaborated with the authors. "I am very impressed

with this study," he added. "It is very simple, but provides a very important insight into cancer etiology."

Tom Hudson, president and scientific director of the Ontario Institute for Cancer Research in Toronto, Canada, who was also not involved, agreed. "The finding is remarkable," he wrote in an e-mail to *The Scientist*. "It is rather difficult to disagree that the correlation is very strong."

Colorectal and basal cell tissue have the highest number of cell divisions of the tissues analyzed and are also the most frequently observed cancer type. In contrast, bone tissue of the pelvis, head and arms undergoes the lowest number of stem cell divisions and has among the lowest observed cancer rates.

The idea that the number of cell divisions and the number of somatic mutations—and therefore, increased cancer risk—are linked is not new, but "the approach taken here to evaluate the level of correlation is original," said Hudson.

Vogelstein and Tomasetti reasoned that because there are minuscule differences in the mutation rates of different human cell types, the number of stem cell divisions within an organ over one's lifetime might explain cancer risk. Most fully differentiated cells, even those that have accumulated mutations, do not seed a tumor because of their short lifespan. But stem cells are longer-lived, self-renew, and give rise to clonal cell populations within a tissue.

The study confirms that some cancers, such as lung, have a large environmental component, and could be largely prevented, noted Vogelstein. "We have to be careful not to make people think that they will get cancer no matter what they do."

On the other hand, the results also emphasize the randomness of certain cancers. For all cancers, the experts stressed, early detection remains vital. "If this work puts more research money into development of better methodologies of early detection that would be great news," said Tomasetti. "Epidemiological studies have shown that lives can be saved through prevention and early detection," added Hudson.

Vogelstein and Tomasetti are now analyzing one of two missing pieces of the study—the rate of breast stem cell divisions. Neither breast nor prostate cancers were included in the study because there are no satisfactory data on the stem cell division rates for these tissue types. The estimation for breast tissue is particularly complex because the rate of division is not linear with time (as it is for colon and other tissues).

This new focus on stem cell division rates "will give us a lens to study many concepts that we have not understood well in cancer," said Parmigiani. "It will likely change the way cancer research and prevention will be done in the future."

C. Tomasetti and B. Vogelstein, "Variation in cancer risk among tissues can be explained by the number of stem cell divisions," *Science*, doi:10.1126/science.1260825, 2014.

Tags

stem cells, somatic mutations, mutation rate, cancer risk, cancer biology, cancer and adult stem cells

mlerman
Posts: 31

January 2, 2015

Cancer genes fall into two main categories: cancer-causing genes, CCG, that drive malignant transformation and maintain tumor growth, and CAN genes that orchestrate local invasion and further spread of metastatic cells. CCG show high mutation rates (~100%) while the CAN genes show low mutation rates (5-10%). The number of genes involved in causation and cancer spread may be estimated from death frequencies as function of age (6-8 genetic steps to death from cancer to be in the range of 3-4 assuming both alleles affected; allowing haploinsufficiency for some of these genes the number may be higher but not to exceed 4-6. This small number is therefore responsible for malignant transformation, initial local growth and finally cancer spread by invasion and metastasis culminating in the death of the patients. The obvious discrepancy between this estimate and the much larger number of cancer genes as reflected in various "gene signatures" (http://cgap.nci.nih.gov/) suggests that most cancer genes associated with a particular cancer are not mutated. The over-/under-expression of these genes results from altered function of the original small set of mutated genes and their downstream targets; among these earliest targets there might be genes ("relay genes") that multiply/diversify the genetic pathways (like HIF 1 and 2 alpha and BHLHB2). The total number of cancer genes assuming there are about 200 different human cancers will not much exceed 6,000-12,000 assuming 10%-5% mutation rates for CAN genes respectively (see estimate below). The number of CCG may not exceed 200. It is important to emphasize the fundamental role of VHL in tumor progression and creation of cancer stem cells

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James V. Kohl
Posts: 204

Replied to a comment from mlerman made on January 2, 2015

January 2, 2015

Re: "It is important to emphasize...creation of cancer stem cells."

They eliminated the creation of sex differences in cell types, which obviously are nutrient-dependent and pheromone-controlled by the physiology of reproduction in species from microbes to man.

See: Signaling Crosstalk: Integrating Nutrient Availability and Sex (microbes)

See: Feedback loops link odor and pheromone signaling with reproduction (mammals)

The link from feedback loops to cell type differentiation in all cell types of all organisms of all species was clarified in the context of protein folding. See: A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping

Population geneticists must exclude any aspect of ecological variation and nutrient-dependent pheromone-controlled ecological adaptations or their statistical analysis will not fit their theories about mutations and the evolution of increasing organismal complexity. For example, see: Mutation-Driven Evolution. Conclusion: "...genomic conservation and constraint-breaking mutation is the ultimate source of all biological

innovations and the enormous amount of biodiversity in this world." (p.199)

If you exclude everything currently known to serious scientists about protein folding, what's left is constraint-breaking mutations and perturbed protein folding that must be beneficial. No experimental evidence of biologically-based cause and effect supports the claim that mutations are beneficial, but they must be.

That means variables such as sex differences in cell types must be eliminated before attempts to portray meaningless results can be made as if meaningless results could ever be meaningfully interpreted by serious scientists. Nei and Nozawa took a similar approach. They eliminated ecological and geographical factors: "...we will not consider geographical and ecological factors because of space limitation. Our primary purpose is to clarify the roles of mutation and selection..."

Tomasetti and Vogelstein try to trick the biologically uniformed majority again. Such tricks will be successful until intelligent serious scientists begin to examine and report cell type differentiation in the context of physical and chemical contraints on the conserved molecular mechanisms that link species diversity in microbes to man. The serious scientists can then claim that pseudoscientific nonsense is a ridiculous approach used by population geneticists to daze and confuse the masses.

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S.Pelech-Kinexus
Posts: 4

January 3, 2015

The work of Tomasetti and Vogelstein sought to quantify the importance of random mutations during stem cell divisions in diverse tissues in the rates of occurrence of various types of cancer in adults. However, their findings have been wrongly extrapolated in the popular literature to suggest that life style and heredity are less influential in the actual incidence of this disease that will afflict more than half the human adult population.

DNA polymerases are among the key enzymes involved in the faithful replication of the DNA sequences in chromosomes. The rate of genetic mutations introduced with normal DNA replication is not insignificant, with different DNA polymerases exhibiting accidental nucleotide base substitution rates in the order of 10(-7) to 10(-8) and even higher. Somatic and germ line cell mutations have certainly been linked for some time to the development of cancers [see for example, Kunkel, T.A. DNA replication fidelity. J. Biol Chem. 279, 16895-16898 (2004).]

Even with high fidelity DNA replication by DNA polymerases accompanied by very efficient proof-reading function that can produce low error rates of 10(-8), with 2.9 billion nucleotide base pairs in the human genome, typically 25 to 35 mutations are generated from each round of cell division. Considering that the adult human body has in the order of 50 trillion cells and most people can live for 70 years or more, this affords ample opportunity for oncogenic mutations to arise. What is most remarkable is that, at the cellular level, cancer is so rare. Many people

never develop the disease.

In addition to defective replication of DNA, genetic mutations can also arise from exposure to radiation and chemical carcinogens during the lifetime of a person. The vast majority of these mutations, known as bystander mutations, are actually benign with little consequence to the health of a person. The critical mutations must occur in very precise locations in the DNA sequences of a relatively small subset of the 21,000 genes encoded by the human genome known as oncogenes. Moreover, these driver mutations must occur in multiple genes in a limited number of possible combinations in the same cell to result in full blown metastatic and lethal cancers. Quantification of which critical mutations emanate from defective DNA synthesis and which arise from environmental assaults will depend on individual circumstances.

Of equal importance to the accumulation of gain-of-function mutations in oncogenes, is the loss-of-function mutations of tumour-suppressor genes. These latter genes encode various enzymes that participate in the repair of damaged DNA as well as other regulatory proteins that inhibit the growth and spreading of cancer cells. Often, the mutations resulting in defective tumour suppressor genes may be hereditary and acquired from conception, and in such an event are present in every nucleated cell of a person's body. However, such loss of function of tumour suppressor genes may be problematic only if accompanied by subsequent mutation of oncogenes. Here again, which driver tumour suppressor gene mutations are hereditary and which are generated spontaneously in only one or a few initiating cancer cells during the lifetime of a person will vary.

Even if cancer driver mutations are generated in cells, they can be often be repaired by many of the proteins encoded by tumour suppressor genes. The lower rates of cancer in humans compared to other species such as dogs, cats and rats may be attributed to higher levels of certain repair and growth regulatory proteins such as checkpoint protein kinases. Within mutated cells, regulatory networks of these proteins carefully monitor the behaviour of these cells and can induce their suicide if their growth and reproduction are sensed to be inappropriate.

Moreover, for the vast majority of early cancer cells that can evade these regulatory controls, the body’s immune system with natural killer lymphocytes and other immune cells can efficiently seek and destroy them. The health of the immune system is highly dependent on environmental factors such as the availability of nutrients, and exposure to toxic substances and other stressful conditions. Consequently, life style works at multiple levels to influence the initiation and growth of tumours and blood cancers.

Certain organs and tissues may be more prone to cancer than others for a variety of reasons besides the actual number of stem cells that they possess. The differential expression of patterns of oncoproteins and tumour suppressor proteins in different tissues and organs could partly account for the differences in the rates of cancer associated with these cell types. Non-stem cells are also able to undergo cell divisions. The skin is the largest organ of the human body, and the most exposed to radiation and noxious environmental agents. The gastrointestinal tract and the respiratory system are likewise highly exposed to the carcinogenic agents that we either consume or breathe in. The organs associated with these systems are amongst the most affected with human cancers. Prostate and breast cancer, which are the most frequent human cancers, were actually

excluded from the Tomasetti and Vogelstein study. Presumably, testes have extremely high levels of germ cells for spermatogenesis, but testicular cancer is one of the more rarer forms of cancer.

Whether driver mutations are produced in the same cell in the right combinations to transform it into a cancer cell may well be a matter of luck. However, there is little doubt from diverse epidemiology studies that life style has a profound effect on the rate that driver mutations are generated, and how the immune system can respond to a growing tumour.

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James V. Kohl
Posts: 204

Replied to a comment from S.Pelech-Kinexus made on January 3, 2015

January 3, 2015

> *Certain organs and tissues may be more prone to cancer than others for a variety of reasons besides the actual number of stem cells that they possess.*

I wrote:

> *If you exclude everything currently known to serious scientists about protein folding…*

These authors eliminated everything known about protein folding, which is linked from nutrient uptake and obesity to estradiol receptor content in tissues most prone to sex differences in cancer rates.

S.Pelech-Kinexus reitterates that fact with extended comments that provide no alternative except to accept Nei's claims about contraint-breaking mutations in the context of his book Mutation-Driven Evolution. However, S.Pelech-Kinexus also notes:

> *The health of the immune system is highly dependent on environmental factors such as the availability of nutrients…*

Is there something not clear about the fact that nutrient-dependent RNA-directed DNA methylation and RNA-mediated amino acid substitutions differentiate all cell types in all individuals of all genera? If so, tell me what is not clear so that I can explain it better than I did with the model and with examples across species in Nutrient-dependent/pheromone-controlled adaptive evolution: a model.

My review was published on the same day as Nei's book: Mutation-Driven Evolution, but no one has compared his conclusion about constraint-breaking mutations to my conclusion.

> *…the model represented here is consistent with what is known about the epigenetic effects of ecologically important nutrients and pheromones on the adaptively evolved behavior of species from microbes to man. Minimally, this model can be compared to*

any other factual representations of epigenesis and epistasis for determination of the best scientific 'fit'.

Instead, we see yet another example of pseudoscientific nonsense about mutations in the context of some cancers, which are not beneficial, while excluding sex differences in cancers, which are not beneficial. The question arises, again: Where can the constraint-breaking mutations be found that contribute to mutation-driven evolution and why aren't mutations differentiated from amino acid substitutions that link the epigenetic landscape to the physical landscape of DNA in the organized genome of species from microbes to man via the bio-physically contrained chemistry of protein folding in all cell type of all individuals of all species?

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ListenUp
Posts: 1

January 11, 2015

It's not "luck" it's what you have been exposed to, IMO.

The increases in cancers have been monumental since atomic testing; nuclear meltdowns like Fukushima and Chernobyl; and since nuclear energy plants have been built around the world.

All of the above distribute(d) "man-made radiation" into the environment and this radiation can be highly carcinogenic and is now ubiquitous in the oceans, air, rain, snow, water, food...causing constant exposure to humans and DNA.

Some of this radiation lasts for up to 250,000 years, and can cause cell mutation.

Dr. John Gofman proved that it only takes one exposure of radiation to a cell to induce a cancerous mutation.

Learn more:

(1) at the highly recommended site www.enenews.com

(2) read the research of Dr. John Gofman

(3) google and read "Cancer Lies" in "majias blog"

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Lovish
Posts: 2

January 15, 2015

Thank you for such an informative article, it certainly helped to understand how Stem Cell Divisions help in explaining Cancer Risk. You can also visit www.yoddhas.com, it is an online support group wherein

such cancer related articles are posted to spread awareness about the disease.

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By Kerry Grens

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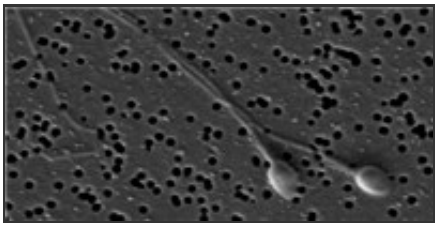

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By Tracy Vence

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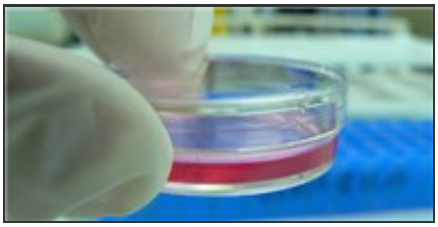

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By Kerry Grens

Embryonic stem cells likely mucked up the cultures used in the debunked "stimulus-triggered acquisition of pluripotency" studies.