Our Evolutionary Origins Expose Cancer's Weakness

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The evolution of cellular regulation has inspired a new model of cancer that predicts ways to attack its weaknesses instead of its strengths.

Medical research has made remarkable progress in combating bacteria, viruses, parasites and the many infectious diseases they cause. However, similar progress has not been made with most common cancers because cancer cells are our own cells, and aren't easily identified as foreign invaders.

However, a new model of cancer based on abnormal traits called atavisms may change our approach to treating cancer. Atavisms are genetic throwbacks that show up unexpectedly and remind us of what we used to be. For example, most of us have two nipples, but sometimes people are born with "supernumerary" nipples along the milk line running from armpit to groin – the region where our earlier mammalian ancestors had functioning nipples. The actor Mark Wahlberg has a supernumerary nipple under his left breast.

Horses used to have five digits on each foot, like the majority of tetrapods, but modern horses normally only have an enlarged middle toe on each foot. Sometimes horses are born with extra toes. The favourite horses of Alexander the Great and Julius Caesar had supernumerary toes.

Atavistic features like supernumerary nipples and toes show up because some genes have been misregulated during the development of the embryo. For instance, a horse embryo starts to develop five digits, but 10–50 million years ago the horse lineage evolved genes that shut down the development of the other four digits and promoted the development of the middle digit. Similarly the human embryo starts to develop a series of nipple pairs, but 50–100 million years ago the human lineage evolved genes that suppress the development of all but one pair of nipples.

When something goes wrong with these suppressors, the extra digits in a horse's foot or the extra nipple(s) in a human are not suppressed and the development of the embryo proceeds according to the default plan before the evolution of the suppressor. In this way, gene misregulation leads to a reversion to earlier atavisms.

When multicellularity began to evolve about a billion years ago, there was an evolutionary struggle between free-living cells, whose reproduction and proliferation was essentially unregulated, and the earliest colonial and multicellular organisms, in which cell proliferation began to be regulated.

The separation of somatic cells from germline cells within multicellular organisms required regulatory mechanisms to force some cells to hand over their reproductive rights to germline cells. Somatic cells had to be regulated to die without proliferating beyond what was needed to protect the germline. This was the origin of programmed cell death.

The controls on proliferation in multicellular organisms involved layers of gene regulation that also controlled somatic cell differentiation. Thus the twin features of cancer cells – non-differentiation and unregulated proliferation – are linked by their common origin about a billion years ago.

We now refer to many of the genes that control cell proliferation as tumour suppressor genes, because when something goes wrong with these genes, cells revert to what they did more than

a billion years ago – the unregulated proliferation of non-differentiated cells -- which in the context of our bodies, we now call cancer.

As we get older, genetic mutations and epigenetic alterations accumulate in our somatic cells. Some viruses and carcinogens can also damage tumour suppressor genes. When this happens, our cells revert to the default plan that was in place before the evolution of multicellularity: unregulated cell proliferation.

The development of what is now the human embryo has been sculpted over hundreds of millions or years. There are about 250 different cell types in our bodies, but our early metazoan ancestors had only a few cell types.

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During the development of an embryo, each cell type differentiates from the original fertilised egg. This differentiation is orchestrated by layers of regulatory genes that turn on and turn off at different embryonic stages, promoting growth here and suppressing growth there.

Cells mature in different ways depending on where they are in the body. Liver cells and colon cells have different jobs to do, so as they mature they go through stages of development that lead to differentiated cells growing in the right place.

However, there is an important difference between the maturation of the entire embryo as a unit and the maturation of individual cells within the developing embryo. The embryo gets only one shot at producing a final body, but some cells are being continuously produced by immature stem cells even when the body is an adult.

When you cut yourself, for example, immature dermal cells start to divide and mature to heal the wound. When the lining of your intestine needs to maintain itself by producing new cells, immature cells beneath the lining produce cells that proliferate and mature. Inside your bone marrow, billions of new cells are produced by haematopoietic stem cells that produce both myeloid and lymphoid cells. Immature myeloid cells mature into various types of blood cells, while immature lymphoid cells mature into the various types of immune system cells.

The cell proliferation that occurs as a normal part of an adult's life occurs in places that are often the most prone to cancer. This is not a coincidence. These are the cells that most easily revert to unregulated proliferation.

Leukaemia and lymphoma occur when your blood or lymph system is flooded with immature blood or lymph cells. I call them "immature" but one could equally call them "atavistic" since they are the result of misregulation of the genes responsible for the maturation process.

What do atavisms and the development of an embryo have to do with cancer? Cancer cells occur when regulatory genes are damaged or improperly expressed. In many ways cancer cells are immature cells – more like stem cells than the terminally differentiated cells we want them to be. Just as the atavistic extra toes on horses are ancient and immature – in the sense of not being fully developed – cancer cells are atavistic in that they are immature cells whose capabilites can be simultaneously associated with incomplete development and an earlier time in evolution when the tree of cellular differentiation had fewer branches.

As cells differentiate and mature, their differentiation pathway goes through stages that reflect the evolution of cellular differentiation. In other words, the maturation of a cell in an embryo has an evolutionary history in which the most recently evolved forms come later during development and are less entrenched in cellular differentiation pathways.

In a new model published in *Bioassays* (http://tinyurl.com/kaetc7u), Paul Davies of Arizona State University, Mark Vincent of The University of Western Ontario and I propose that these recent cellular capabilities are less entrenched and are thus more susceptible to damage due to a lack of repair and the accumulation of somatic mutations with age.

Our atavistic model is based on increasingly precise knowledge about which of our cells' capabilities have recently evolved and which are ancient. With this knowledge, our model makes predictions about which capabilities are lost in cancer cells and the order in which they are lost.

Our model also identifies the strengths of cancer as the cellular capabilities that were established and became entrenched more than a billion years ago. Non-regulated cell proliferation is one strength, and is therefore not a strategic feature to attack. For four billion years our cells have learned to protect their ability to proliferate. This suggests that current therapies have been targeting cancer's strengths, such as cell proliferation, rather than its weaknesses.

In our new model, the weaknesses of cancer are the loss of cellular capabilities that evolved most recently – in the past 500 million years or so. For example, the most recently evolved part of the immune system, adaptive immunity, doesn't work well in tumours. This is called immunosuppression. Newer aerobic respiration doesn't work well in tumour cells either – cancer cells revert to aerobic glycolysis.

We hypothesise that the most recently evolved DNA repair mechanisms don't work as well as the older, more entrenched repair mechanisms. If recently evolved cellular capabilities are compromised in cancer cells, then their absences are weaknesses. We need to exploit these weaknesses by creating challenges that only normal cells with their full complement of capabilities can survive.

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