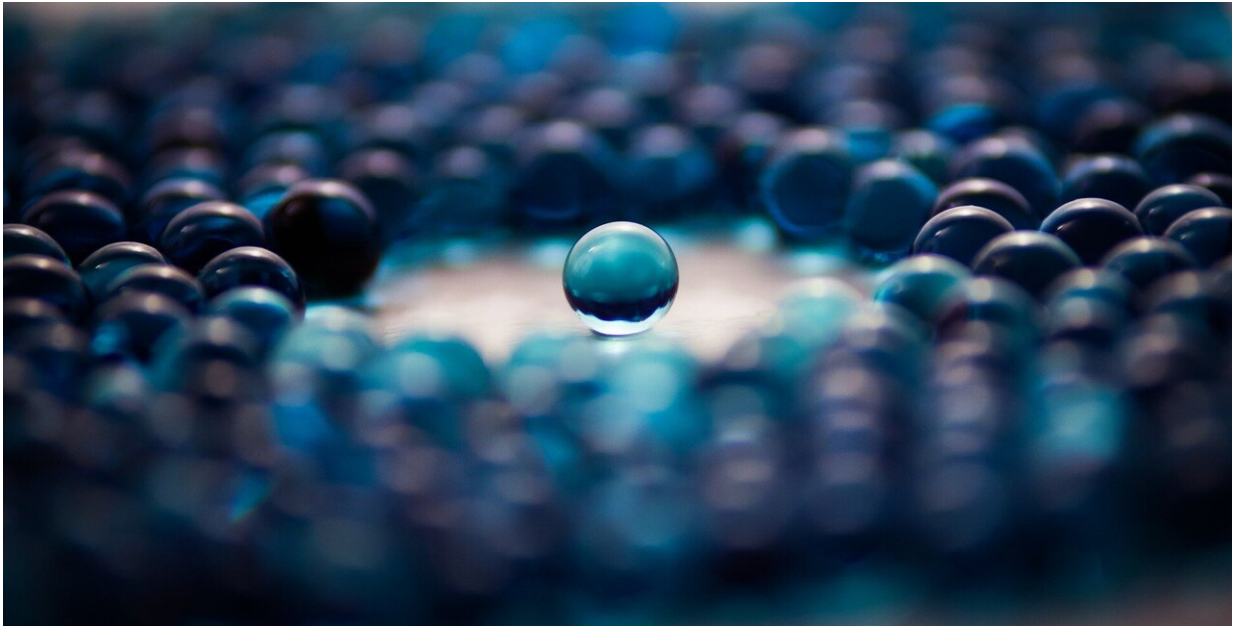


# No tumor is an island

June 28 2019, by Dr Kat Arney

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For decades tumors have been viewed as 'other'—malignant, unruly growths that are distinctly separate from the ordered physiological system within which they live. This view has shaped our approach to treat cancer: cut it out if it's small enough, zap it with radiotherapy, or attack it with ever-more-precisely targeted drugs.

However, this perspective has been changing with the recognition that cancer is a disease of the whole body and that a tumor is an integral part

of the host.

## What is normal, anyway?

The rise of large-scale high-throughput genomics has provided researchers with a detailed understanding of cancer-related mutations—from childhood tumors with relatively low mutational burdens to advanced metastatic cancers shot through with tens of thousands of [point mutations](#), deletions, insertions and large-scale chromosome rearrangements. These findings have contributed to a view of cancer cells as very different from normal cells.

However, sensitive next-generation sequencing of very small samples of normal tissue has recently revealed that supposedly healthy tissues are in fact composed of a patchwork of mutated clones—a finding that would have been disguised as noise in the larger, homogenised samples of 'normal' cells that are usually used as controls in genomic experiments.

In 2015 Inigo Martincorena and colleagues at the Wellcome Sanger Institute found that normal [sun-exposed skin cells have a significant burden of genetic damage](#), with a quarter containing what would be considered to be a cancer driver mutation if found in a tumor biopsy. Three years later, [the same team found](#) that each square centimetre of normal oesophageal tissue contains tens to hundreds of mutant clones, whose number increases with age. A significant proportion of these cell patches carry mutations in Notch1 and p53, which are usually thought of as classic cancer driver mutations. At the same time, George Vassiliou's team at the Sanger Institute has found that normal blood is actually a [soup of distinct clones carrying diverse mutations](#), which become more prevalent with age. Many of these mutations would be considered to be drivers of leukaemia.

These findings have relevant implications for cancer diagnosis and

therapy. For example, the presence of apparent cancer driver mutations in normal tissue could provide false-positive results for DNA-based liquid biopsy diagnostic tests and mislead the selection of targeted therapy. [The discovery by Martincorena and colleagues](#) that Notch1 mutations are more prevalent in normal oesophagus than in tumors also suggests that some alterations might even be protective, raising questions about the best use of therapies designed to target these specific drivers.

These observations fit with classic combinatorial models of cancer development, such as the "[Vogelgram](#)," in which bowel cells must gather a particular set of mutations to make the leap toward cancer, although these mutations do not necessarily have to happen in a specific order. However, Ruben van Boxtel and colleagues in the Netherlands [published striking results](#) in 2016 showing that mutations accumulate in normal stem cells in the liver, large intestine or small intestine at a rate of around 40 per year throughout life, despite these tissues having very different cancer incidence rates. These findings suggest that there must be more to the transformation from healthy cell to cancer than the simple accumulation of a certain number of genetic changes over time, raising major questions about the nature of tumor formation and growth.

For example, are the natural selection pressures that drive the initiation and evolution of cancer different in distinct tissue types? Are some tissues – [or even people](#) – highly tolerant of mutations while others eliminate damaged cells and control clonal growth? And, if so, which ones are more resistant to cancer? To what extent do neighboring clones keep each other in check or compete for resources? Is cancer inevitable once a certain "mutational checklist" has been ticked? How do cancer cells manage to "cheat the system" in these various environments to grow out of control? And, ultimately, what turns a "sad cell" (i.e. one containing genetic damage but otherwise apparently healthy) into a "bad cell" that grows into a malignant cancer?

## Nature and nurture

The idea that conditions within the host environment can either [encourage](#) or [hold back](#) the development of cancer is not new. Back in the 1990s, [Mina Bissell and her colleagues showed](#) that cancer cells will behave as normal tissue if placed in the constraining environment of a laminin-rich three-dimensional gel culture, but will flip back to a malignant phenotype when this new stable 'home' breaks down. The [cancer-promoting role of inflammation](#) is also well known, and has been further supported by [intriguing recent results](#) from Mikala Egeblad and her team at Cold Spring Harbor Laboratory pointing to a role for neutrophil activation in reawakening dormant cancer cells to trigger metastasis.

The role of the microenvironment around a solid tumor is being increasingly appreciated. The [stroma](#) – a diverse collection of items including cancer cells, immune cells of many types, fibroblasts, blood vessels and extracellular matrix, soaked in a bath of cytokines and signalling molecules—is the most important component of this microenvironment. A typical pancreatic tumor comprises around 10% cancer cells, with the bulk being made up of [normal cells](#) that support or fight against them.

The concept of cancer as the "wound that does not heal," [formalized by Harold Dvorak in 1986](#), still [stands up today](#) and deserves closer attention as the focus shifts from considering single cancer cells to contemplating the ecology of the tumor microenvironment. [Recent work from Gerard Evan and his team](#) shows that expression of the oncogenic transcription factor Myc in pre-cancerous lung adenoma cells is enough to trigger inflammation, growth of new blood vessels and suppression of normal immune responses in the surrounding lung tissue.

This rapid stromal remodelling drives a usually benign adenoma to

become an aggressive cancer, while switching Myc off reverses these changes. In healthy tissue, Myc plays a pivotal role in directing the complex biological processes required for wound healing and regeneration, suggesting that its aberrant activity in cancer leads to a strange, corrupted recapitulation of normal healing processes.

These findings suggest that any factors that trigger or exacerbate tissue damage or inflammation could contribute to tumor growth. Conversely, finding ways to control inflammation and wound healing could be translated into [useful therapeutic approaches](#).

## **The immune system: friend or foe?**

The presence of immune cells within tumors was first [noticed by Virchow in the 19th century](#). More than 150 years later, [James Allison and Tasuko Honjo won a Nobel prize](#) for their groundbreaking work underpinning the development of immune checkpoint therapy.

The success of checkpoint inhibitors (and, to a lesser extent, [CAR-T cell therapy](#)) highlights the benefit of harnessing the power of the adaptive immune system to recognize and attack rogue cancer cells. But far less is known about the role of the immune system in tumor initiation and progression, particularly the idea that immune surveillance protects against cancer, which was [first put forward by Paul Ehrlich in 1909](#) and is still a [hot topic in research today](#).

Despite the attractiveness of this concept, we are lacking hard data to prove that the host immune system actively seeks out and destroys rogue cells during the earliest stages of cancer initiation. By contrast, evidence shows that the actions of the immune system, especially inflammatory processes, have an important role in encouraging "sad" cells to become malignant. As noted by [Fran Balkwill and Alberto Mantovani in 2001](#), "If genetic damage is the 'match that lights the fire' of cancer, some

types of inflammation may provide the 'fuel that feeds the flames.'"

## **From micro to macro**

The wider ecosystem of the body also influences cancer growth, metastasis and response to treatment. Sex hormones drive the growth of many cancers and can be [effectively targeted with hormone-blocking therapies](#), such as tamoxifen or anastrozole for estrogen-responsive breast cancer and bicalutamide and abiraterone for prostate cancer. The insulin-like growth factor (IGF) family and its receptors have also been implicated in several tumor types, most notably bowel cancer, although [efforts to target these proteins have so far been unsuccessful](#).

Circadian rhythms affect many biological processes involved in cell maintenance, repair and response to cancer treatment (for example, [repairing damage caused by cisplatin chemotherapy](#)). Perturbation of several genes that control circadian rhythms increased cancer risk in animal models. Shift work was classed by IARC as "probably carcinogenic to humans" in 2007, although this risk has been [questioned over the past decade](#) as new studies emerge.

The microbiome is also emerging as an [important area in cancer research](#). Mel Greaves has argued that exposure to an appropriate range of microbes in early life is [protective against childhood leukemia](#), whereas Jennifer Wargo and others have begun to investigate the [impact of the microbiome](#) on the responses to chemo- and immunotherapy. Gut microbes could also alter the availability of certain nutrients to the host (and therefore to tumors), produce potentially carcinogenic compounds and manipulate the host immune response—all of which could influence cancer initiation and growth.

The metabolism of cancer cells depends on energy and nutrients provided by the host. There is growing evidence that certain types of

cancers suffer from '[metabolic addiction](#)', becoming overly-dependent on specific nutrients, particularly amino acids such as histidine, glutamine, asparagine and serine. There is also interest in the role of altered glucose metabolism in fuelling cancer growth ([the Warburg effect and other mechanisms](#)) and in the link between [high dietary fructose intake and non-alcoholic fatty liver disease and liver cancer](#). More broadly, the connection between obesity and cancer is an ever-expanding research area. Although more work needs to be done to understand the range of metabolic alterations that occur in tumors, limiting the availability of key nutrients or targeting the enzymes that produce them might be an effective way of "starving" cancer cells.

Exosomes are emerging as another area of research focus. These small packets of RNA and other molecules transmit information around the body and have been proposed as a way in which cancers "seed" distant parts of the body to make a comfortable "soil" for future metastases. However, one of the most prominent studies in the area—a [2012 paper](#) showing that exosomes from highly metastatic melanomas could "educate" healthy bone marrow cells to enhance cancer spread—could not be replicated by a different laboratory.

## **Taking a holistic view**

Much work has been done to unpick the complex ecological and evolutionary mechanisms that influence cancer growth, spread and response to therapy. However, too often these experiments rely on "dead" biology, studying fixed samples of tumors and tissues gathered at specific time points (for example, prior to therapy and after relapse). These snapshots do not capture the complex interactions and selective pressures that have occurred between cancer and host over time.

Cancer genome sequencing projects have grown exponentially over recent years thanks to advances in DNA sequencing technology and

bioinformatics. These projects have gathered hundreds of thousands of tumor samples and dissected genetic heterogeneity down to the level of a single cell. But taking such a gene-centric view means that the field has tended to focus only on mutation and missed out on the equally important aspect of natural selection of cell phenotypes within a dynamic environment.

Focusing exclusively on genes also tends to overlook the role of epigenetic alterations affecting proliferation, drug resistance and other cancer phenotypes, which cannot be detected through simple genome sequencing. Just as epigenetic modifications lie at the heart of cell and tissue plasticity during normal development, epigenetic changes allow cancer cells to display different behaviours and characteristics—such as epithelial-to-mesenchymal transition—even in the absence of underlying genetic mutations. The most well-known epigenetic mark, DNA methylation, can be passed on through cell division and potentially provides the kind of heritable variation on which natural selection can act.

As [Isaac Berenblum](#) wrote in 1974, "we find ourselves at the present time in the era of molecular biology, and we are perhaps unduly influenced by the genetic code as the dominant principle in biology. Perhaps, in a decade or two from now, the dominant principle may shift to another plane, which in turn will influence our speculations about tumor causation."

More than four decades later, the primacy of genetics is finally giving way to a view of cancer as an integral part of a physiological system—the body of the host—rather than an almost alien "other." It is time to reclaim the concept of holistic medicine, which has been hijacked by alternative therapies, to describe a view of cancer that incorporates the whole body (along with its resident microbes) in order to understand how the disease starts and spreads, and how to treat it



more effectively.

Beyond developing drugs that target the products of the mutated genomes within a tumor, a growing body of evidence suggests that there is untapped potential in developing therapies that manipulate various aspects of the host environment to make it inhospitable to [cancer](#) growth. From boosting the ability of stromal cells to enforce the "social norms" of healthy tissue and bring rogue [cells](#) back in line, to altering the local acidity of the tumor microenvironment, tweaking the diet, manipulating the microbiome and resetting the body clock, there are many approaches that deserve more thorough exploration.

**More information:** Francis Blokzijl et al. Tissue-specific mutation accumulation in human adult stem cells during life, *Nature* (2016). [DOI: 10.1038/nature19768](https://doi.org/10.1038/nature19768)

Héctor Peinado et al. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET, *Nature Medicine* (2012). [DOI: 10.1038/nm.2753](https://doi.org/10.1038/nm.2753)

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