Evolution of action in cells and organisms

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Vineis and Berwick (V&B)\(^1\) raise important issues about the ‘Darwinian’ nature of cancer. It is a story of the evolution of populations of people and of cells. Cancer involves somatic changes in cells that must live, cooperate, and compete with other cells. The distinction between cells and organisms is in many ways a human rather than a biological one.\(^2\) Cells are organisms that, in some instances such as in the bodies of vertebrates, often happen to be stuck to each other. But even free-living single-celled species, such as bacteria, interact with each other (and even sometimes stick to each other!).

The great insight of AG Knudsen\(^3\) transformed cancer research, and after his paper and some observations that confirmed the general idea in regard to retinoblastoma, it was steadily discovered that cancer cells are genomically different from the host’s other (normal) cells and that cancers evolve as a descendant clone of their initiating single cell. This is an evolutionary argument even when not explicitly couched in Darwinian terms. Vogelstein and his collaborators made somatic evolutionary progression a canonical view of cancer directly related to staging.\(^4,5\) Indeed, somatic mutation may be a much more important cause of disease than cancer alone.\(^6\) The story is not yet entirely clear even in the case of cancer,\(^7\) at least in major part because we still have relatively little idea about the degree of normal somatic variation, an important but as yet unavailable comparison base (though it is starting\(^8\)).

One reason cancer must usually be an evolutionary phenomenon is that misbehaving cells are not generally compatible with embryo genesis. This is why we do not inherit a ‘cancer’ genotype, most cancer-related mutations are cellurally recessive, and loss of heterozygosity or additional mutations at other genes occur somatically. That was at the heart of Kundson’s insight (and, in a way, Macfarlane Burnet’s earlier ‘forbidden clone’ hypothesis must have been a factor in Knudson’s thinking since it was in the air at the time).

Precursor growths, of which the classic instance were colorectal polyps, were long thought to raise risk at least in part by increasing cell divisions during which subsequent

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\(^{5}\) Hall BG. Spontaneous point mutations that occur more often when advantageous than when neutral. *Genetics* 1990;126:5–16.


\(^{13}\) Hallgren M, Jirtle R. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. *Nutrition* 2004;20:63–68.


mutations could occur. That idea became even clearer when it was shown that tumours are clonal and by recent tumour gene expression profiling. The evolution of drug resistance by gene amplification and the ability to metastasize and colonize specific sites also clearly imply evolution. I would quibble with V&B’s statement, if I understand it, that the role of selection of mutated cells has not been clearly investigated, because at least in principle this has been a main focus of cancer genetics for many years. But this is minor relative to their main point that not all cellular misbehaviour need be proliferative growth, but includes other things like unhealthy norms of reaction. In a time in science that seeks simple (if not simplistic) Darwinian explanations, it is important and quite within the range of normal biology and evolution that not all selection has to do with differential growth.

V&B have added an additional important twist to the story, which should surprise no evolutionary biologist, and they provide some likely examples. The idea that not all mutations are equivalent with respect to response to environments is a direct extension of what is widely known about genotypes among organisms. That the finger points to environment and not just genes is clear, as they argue. I think they should have cited an era of extensive and influential work 20–30 years ago that made this very point (e.g. ref. 9, 10, among a wealth of others) but in the short memory of contemporary science may have largely been forgotten. At the time, Doll and Peto argued from regional variation in cancer prevalence that most causes had to be environmental, but we have a more nuanced understanding of basic cancer biology today. Environment is still important, perhaps paramount for many cancer types, but as V&B say, environments may trigger different alleles differently.

V&B stress alleles that arise somatically. But there must also be considerable differences among populations in the susceptibility alleles they carry, and these can be part of the story by which different people respond differently even to the same environmental triggers. At least some of the variation is undoubtedly heritable. This is implied by data such as the population variation in the mutations and their frequencies in known susceptibility genes like BRCA1/2, and colorectal cancer related genes, not to mention...the rather obvious case of skin cancer and pigmentation genetics. And these usually account for only a fraction of the familial (and hence at least partly inherited) risk. There might be some relevance here to the idea of Mendelian randomization as a kind of test, when enough becomes known about putative risk factors that might have differential cellular response.11

Epidemiologists like to live within the space of tractable models, and V&B give some examples. However, for a long time it has been clear that cancer was not a simple 2 or 3 stage process at the gene level even if such models can be statistically fitted to empirical data at the trait level, because both among cells and in susceptibility variation among individuals cancer is genetically more like a quantitative many-locus trait than a simple one.12,13 The price of tractability is oversimplification, which is alright if it leads to success, but not if it leads to hopes for unrealistically simple intervention strategies. We know things are much less replicable than such simple mathematical models suggest, through decades of experience mapping cancer and countless other complex traits, which find some culpable genes but account for only a small fraction of the overall genetic risk.

Evolution is always with us, and while Darwin showed us the tiger, it is not yet clear even after 150 years whether we have the tiger by the tail or it has us. That these things are not obvious to everyone, at least in general terms, reflects a failure of our educational system, with a short memory and too much technical specialization, which drives out a more nuanced biology of which evolution is a vital part. V&B have done well to lay out many aspects of the reasons why cancer is an evolutionary disease par excellence. One can hope they are wrong about the daunting complexities they raise—but the evidence supports their concerns, and if that is the reality we will simply have to face it.

References