Cancer – Pretty Evolvable, But Not Quite There…Yet!

Arjun Krishnan, Janani Ravi
Centre for Biotechnology, Anna University, Chennai

"Natural selection will tend in the long run to reduce any part of the organization, as soon as it becomes, through changed habits, superfluous, without by any means causing some other part to be largely developed in a corresponding degree."

Charles Darwin, The Origin of Species

The *selfish* gene, as we know the *replicator*[φ1], harbors the properties of fidelity, fecundity and longevity, and it could be defined as any portion of chromosomal material that potentially lasts for enough generations to serve as a unit of natural selection; thanks to Dawkins[φ2].

All along the history of life we see the gene colluding with others of its kind (different in potential) helping each other in achieving multiplicity, in terms of their own structural/functional properties and their products (ribonucleotide chains[φ3] or polypeptides)[φ4]. Cells and cell-aggregates (tissues), and finally, bodies were formed to act as vehicles to protect, carry, replicate and transfer these genes. Along the process, these genes evolved by acquiring mutations (hence varying). Successful gene pools[φ5] were selected for and stably inherited.

Gene systems use their environment to acquire mutations and hence vary - the very first step in evolution. And, *cancer cells* vary to a stage where they can exhibit more variation[φ6], developing (greater[φ7]) *evolvability*[φ8]. A brief detour may be required to make this point clear.

Evolvability is the capacity to evolve, to generate heritable, selectable phenotypic variation. It does two things: one, it reduces the potential lethality of mutations, and two, it reduces the number of mutations needed to produce a novel phenotype. But, evolvability seems to confer future rather than present benefit to the individual, which would violate the fact that evolution has no foresight. Nature not only selects a variant but also selects that variant's very ability to vary, which almost seems like saving for the future.

Let us, however, look at it this way. There are several ways in which genetic mutations occur. Random changes along the ladder is just one of the ways. Mutations also occur based on genetic recombination, transposition and horizontal gene transfer, allowing relatively large chunks of genetic information to be shuffled or substituted for one another along the DNA chain. This very ability to reorder genes or to cause large-scale genetic change is by itself a genetic trait, *a trait that is subject to selection* like any other. Evolvability is quite an observable phenomenon, seen, for example, in the war between pathogens and the immune system[φ9].

Getting back to the topic, cancer cells are hardy, rough guys and carcinogenesis is a take-over; these cells grow and out-grow, resisting medical efforts to contain them[φ11], ultimately killing the patient. The abilities of malignant cells to grow, hijack and use up the body's resources, and acquire (multi-) drug resistance have been looked into. What has caught our attention is the fact that tumour cells profit from mutation and other types of genomic instability, enabling them to *evolve readily*, something we have been discussing all along. They eventually acquire a greater ability to vary, and hence, to evolve. As a robust system, a cancer cell exhibits tolerance but it also has in it a tendency to cause genetic changes, which in turn increases the chance of stumbling upon an improved or novel trait.

Carcinogenesis clearly represents a strategy in evolution- it almost gives us a glimpse of what metazoan cells would evolve into. Cancer is almost there, if only it wouldn't ultimately kill. We know of the bacteria in our gastro-intestinal tracts that have evolved to not harm the host and just use it to replicate and spread. Carcinogenesis, like these parasites (only analogously), could evolve into a form that would allow greater, yet controlled metastasis and stable colonization and finally, horizontal and vertical transfer. This new process could eventually replace our present mode of restrained cellular replication and, in effect, that of the individual. More, and yet, optimized variability could confer greater robustness to the system making life possible in more diverse environmental conditions.

Probably, every leap in evolution is characterized by an increase in the evolvability of the life forms, which confers increased variability. What we see now, in the form of cancer, is just inappropriately constrained variability that causes lack of stability - something you'd observe in cheating and other antisocial behaviour. In the present case, evolvability evolves to be suppressed when the trait confers short-term individual advantage and long-term population disadvantage. What it might become can well be where the next step in evolution could take *us*!

Footnotes

φ*i*: Did you notice the *copyleft*? (You think it's imaginary, don't you?)

φ0: Statutory warning: footnotes are terrible distracters!

φ1: Let's get this clear: calling the gene 'selfish' and thus attaching a motive and purpose (of replication) to it is *not* to scientific convenience. It is not because it is a gene that it can replicate but because it has high copying fidelity that it is a gene.

φ1.618: Phi was chosen to add *beauty* to the work! Few would've already appreciated it- those that knew that phi represents the *Golden Ratio!*

φ2: Thalaivaa!

φ3: Many genes code for RNA molecules which function in various information processing steps, interference RNAs for example.

φ4: Here, we wish to digress to bring up the fact that the earliest biotic earth was an 'RNA World' (with ribonucleotides capable of information storage, replication and catalysis, 'molecular fossils' of which still prevail in the form of catalytic RNAs) and there is ample evidence to corroborate that proteins predated DNA. However, for our discussion of a present day scenario, these facts are only remotely relevant.

φ5: An apparent contradiction to the definition of the gene as the unit of natural selection. It's quite an argument; discussing in person might help!

φ6: No, here and anywhere else, we're not referring to cancer development as an evolutionary process within the body of an organism, shaped by the somatic environment. We look at carcinogenesis as a way of evolution itself. Hope the fog clears…read on…

φ7: To be precise, it is essential to say 'greater' because all gene systems are evolvable; Evolvability is one of their inherent properties. Cancer cells only achieve more of it.

φ8: Something fans of ‘artificial life’ will appreciate most. New comers, lookout for ‘Tierra’, ‘Thomas Ray’, ‘Virtual/Artificial Life’, ‘Thala’φ2.

φ9: For example, the codon usage within the influenza hemagglutinin protein seems to be biased to favour more rapid antigenic drift. In HIV-1 protease, the probability of mutation is not randomly distributed within the structure but rather concentrated at sites that alter the geometry of the protein-binding domain, conferring significant propensity for antigenic drift. A more abstract example would be the existence of memes _10, as in humans (we guess it is ok to say this of other developed life forms like animals, insects etc.) Wow!

φ10: Formally defined as “a contagious information pattern that replicates by parasitically infecting human minds and altering their behavior, causing them to propagate the pattern”, a meme is just any piece of information and they represent *everything* that we think, believe and talk.

φ11: Therapeutics confer selective pressure on the evolvability of tumour cells as they do to pathogens, and this driving force for drug-resistance or heterogeneity in the case of malignant cells and antigenic drift in the case of pathogens, should be considered in drug and vaccine design efforts.