CANCER, AN EVOLUTIONARY DEVELOPMENTAL PROCESS IN MULTICELLULAR LIFE M.R.S. António[1] and D. Schulze-Makuch[1], [1]School of Earth and Environmental Sciences, Washington State University, Pullman, WA 99164, USA (quimarina@wsu.edu; dirksm@wsu.edu)

Introduction: Evolution is by definition, work in progress. Natural selection does not have any foresight, nor does it need it in order to be widely successful in maintaining life on this planet. Evolution is also 'cheap'. New modifications to existing processes are usually not built from scratch, but rather constructed on what is already there. This leads to 'imperfect' solutions, with glitches and plenty of space for further improvement. And that is the exact strength of evolution, it is never finished. Perfect solutions to present conditions would function if natural selection would be constant. But change, at least on this planet, is a predictable event and therefore the more flexible the solution, the better the chances that a particular life form will continue to flourish. Building on ancient solutions is also beneficial, because these solutions have proved successful for thousands, millions or billions of generations. A new solution is invariably risky and often costly.

Developmental processes such as embryogenesis are incredible examples of the intricate paths evolution builds upon through time. During human embryogenesis the initial amorphous mass takes various shapes (very similar to other vertebrates' embryogenesis) through cycles of expanding and receding cell movements. In order to achieve the final human morphology, many of the initial morphologies could be discarded, yet they are not. Recreating a unique human embryogenesis would probably be possible but utterly risky. Once nature finds a successful pathway, it tends to hold on to it. After all, it is a rare and valuable moment that life will adopt until changing times make it obsolete and better solutions are found.

The complexity and resilience manifested by cancer are far too intricate for its classification as a cellular disorder disease. In the apparent chaos caused by a malignant tumor, the cellular machinery is subverted, organismal function halted and the best intelligent attempts are deceived, simultaneously. Our long and costly attempts to defeat this 'disease' are far from solving the problem, with the result that cancer has now surpassed heart disease as the number one cause of death within the industrialized world. The cause for this failure may lie in a conceptual misunderstanding of what cancer really is, rather than on technical limitations. Cancer is currently understood as the result of a cellular disorder (caused by carcinogenic agents in some cases worsened by a genetic propensity either to error or defective repair mechanisms) [1]. The gross accumulation of errors often results in the deregulation of the cell-cycle control. [2] The cancer cell becomes at this point unresponsive to inner and outer cell death signaling. Although despite all chaos, cancer cells are often able to replicate (with numerous mutations) and expand their number. The current argument is that some of the mutations confer some advantage to the host cancer cell and through natural selection that cell survives and replicates its genetic information further, and the process repeats itself in the next generation, until a metastatic ability is developed and again naturally selected. The cancer cells that resist all the inner attempts of destruction plus the chemical and radiation assault inflicted by chemotherapy and radiotherapy are subliminally fit and become unstoppable with a tragic ending. This explanation makes sense and explains most observations. But, it is not the most parsimonious explanation to the phenomenon we are observing.

A closer look: A closer look at the stages of cancer is able to shed some light. Cancer can easily be triggered in laboratory animals (although the aggressiveness of this induced cancer tends to be diminished, when compared to natural occurring cancer, which results in many cases in a natural remission of cancer) by the use of known carcinogens. This indicates that we understand fairly well the causing agents of cancer. The common perception though is that carcinogens increase the mutagenic rate. That is not the case for a large number of cancers. What carcinogens do is to increase the stress and metabolic rates, thus ultimately causing a higher mutation rate (or failure to repair mutations) along the line. So, the point is that a higher mutation rate is a consequence and secondary effect of cancer, not a necessary condition. In fact there are many cancers which do not display a significantly higher mutation rate than a normal cell. Once a tumor is formed, the most potent immunosuppressor described to date (TGF-β) is released in copious amounts by the cancer cells (this is in fact one of the ways cancer can be spotted through blood analyses). This is immediately followed by a loss of the inter-cellular receptors that allow for intercellular communication and a deactivation of the pathway that impedes cells from constraining each other's spaces, effectively allowing cancer cells to crawl over any neighboring cell. Cancer cells then reroute or even reconstruct surrounding blood vessels to allow for their own survival (which is highly demanding in energetic terms due to the higher metabolism), which is the beginning of the

most devastating effects of cancer, which deplete neighbor cells from resources, ultimately causing tissue death and disruption of the host organ function. A malignant tumor will sooner or later enter a metastatic phase in which the cancer cells detach from their original location and are carried through those same blood vessels they have conveniently reconstructed to other parts of the body. It is important to note that during this phase cancer cells do not seem to be heavily restrained in their new locations as any type of cancer can metastasize into virtually any other organ and efficiently survive and proliferate in the new environment. The secondary tumor then employs the same fundamental strategy adopted by the initial tumor, despite the fact that in the mean time this new tumor has accumulated a large number of mutations. The repetition of these events can quickly result in a systemic failure or vital organ failure. The current interpretation argues that this happens in a stepwise fashion because natural selection has eliminated the less efficient lineages and we are left to see the ones which have an effective outcome.

The problems: This explanation is immensely unsatisfactorily for a number of reasons. The occurrence of beneficial mutations is a very rare event, only enhanced by sheer numbers. The replication rate of cancer is high when compared to a normal cell, but it is orders of magnitude less than for common pathogens such as bacteria and viruses. If cancer evolves at a reasonable rate, bacteria and viruses should have eliminated the human race a long time ago. If these pathogens developed the resilience that cancer displays, every common cold and infection would certainly result in death. Let there be no doubt: cancer has an (apparent) astonishingly high evolutionary rate. The second reason why the classic explanation for cancer is unsatisfactory is because it severely underestimates the complexity of each single accomplishment. The timeline and stepwise outcome of cancer is better described by a developmental process than by an evolutionary one. Each single cellular pathway cancer disrupts or subverts belong to the most complex pathways optimized by evolution. How could cancer break one after the other in a fragment of a lifetime? Just as embryogenesis, chaos quickly and intricately develops into an apparent self-organization. The difference between a developmental process and an evolutionary process is time. We all know it is unreasonable to expect that an eye can form from an amorphous mass of cells within a few months. This development has to have evolved over millions of years. The new EvoDevo (Evolutionary Developmental Biology) science shows us how embryogenesis is a flash through millions of years of evolution. Despite the detrimental effects, cancer is a definite candidate of an EvoDevo process.

A parsimonious explanation: Given all of the above, the assertion that cancer is not a disease but instead an ancient programmed cell response should come as no surprise. Cancer is better explained as a cellular response to a prolonged form of local cellular stress (real or perceived as real by the afflicted cells). It is important to note that the stressor often targets specific types of cells (or with a particularly high intensity). A malignant tumor will develop when a cell or particular group of cells are under prolonged stress conditions with a combination of unresponsiveness from the immune system (either by failure to detect the threat or inability to stop it). The cell can under these circumstances activate an extreme survival pathway, which can be currently observed in biofilms and communal unicellular aggregations [3]. These aggregations are composed of a varied number of species, often belonging to different phyla or even domains. If the environmental conditions (abiotically or biotically triggered) shift in disfavor of a particular species beyond a point where they would be better off on their own, they will detach from the aggregation and drift (these often occur in aquatic environments) to another location [4]. Cancer cells may be the result of the activation of a survival plan that outdates multicellularity. In order to escape and attempt autonomous survival the disconnection from the surrounding cells is needed, as well as a change in location. This survival plan is beneficial when the cells do have a chance of succeeding elsewhere on their own and by escaping a certain death. It is however a missfitted approach (as far as we can tell) in a terrestrial multicellular organism. Although, this solution is deeply imbedded in the root of multicellularity and given that only particular circumstances activate it, usually at a post-reproductive age, natural selection does not have much of a chance to exert its effect. Cancer is in essence a demonstration of life's resilience power. Biology makes no sense unless under the light of evolution, cancer included.

Given the universal nature of cancer it is reasonable to assume that this dysfunction could plague the unicellular to multicellular transition. On the other hand, it is also possible that multicellularity will eventually evolve into a cancer free life form, given that the fitness of the organisms would certainly increase.

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