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Old Ideas Die Hard, Particularly in Cancer Biology

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Cells in a clonal population always display substantial phenotypic heterogeneity of non-genetic origin (Brock, Chang, & Huang 2009). Heterogeneity arises from the inherent stochasticity of molecular interactions, including gene expression that produces a large variety of cell phenotypes. It has been assumed that constraints and forces of selection shape this heterogeneity (Bizzarri 2018). These forces probably arise from interactions between the cells locally and at the level of tissues but may be intrinsic, depending on the individual life trajectories within the cell population. There are also extrinsic forces, such as physical parameters and nutrient availability. Together, they may act on the diversity of cell phenotypes and produce new populational structures and tissue organization. This is a typical Darwinian mechanism based on random variation and selective stabilization. It has been proposed that normal cell differentiation and embryonal development but also pathological processes such as cancer proceed through a Darwinian mechanism (Kupiec 1997; 2020; Paldi 2020). Both aspects have been discussed in *Organisms*.

The fact that the cells proliferate and generate a heterogenous population spontaneously without the need for external instructions or signals is now well known. However, the idea that this represents a fundamental feature (Montévil 2016) has some difficulty in being accepted. The typical way to frame the issue of heterogeneity is to implicitly assume that cell populations are homogeneous on their own and that diversity is generated by specific mechanisms. For example, in the case of normal development, it is typically assumed that cells differentiate or divide only when they receive an external inducing signal. This is a classical deterministic reasoning that has been challenged (Sonnenschein & Soto 2021). A corollary of this deterministic logic is that cellular diversity found in clonal populations of cancer cells must have specific cell intrinsic causes. Indeed, if the origin of cancer lays in genetic mutations that empower an individual cell to proliferate faster than others, as stipulated by the somatic mutation theory (SMT), then the emergence of more malignant subclones must also result in the accumulation of more genetic mutations. Although SMT faces a number of conceptual contradictions inherent to the theory itself and directly contradicts many essential observations (Sonnenschein & Soto 2020), it still remains hegemonic. Attempts are regularly made to update it, typically using *ad hoc* propositions to resolve some of these contradictions. They also usually reinforce SMT deterministic nature while pretending to introduce some Darwinian logic.

A recent example of such an *ad hoc* proposition was provided by Khatib and colleagues in a paper entitled

"Understanding the cause and consequence of tumor heterogeneity" (Khatib *et al.* 2020). The authors examine the origin of cancer heterogeneity, and ask a typically SMT-inspired question: "Does a common mechanism exist that drives cancer heterogeneity to achieve the fitness and survival of a given cell community?" The question itself—putting aside its anthropocentric flavor—is founded on several implicit assumptions. First, it postulates the existence of specific mechanisms shared by all cancer types that generate cell heterogeneity on purpose. Second, the cancer cell community is supposed to have its own fitness. Unfortunately, these assumptions are not made clear, hence no arguments support them. The authors favor a superficial analogy involving forest fires and cell death. Namely, since natural or manmade fires promote biodiversity in natural ecosystems, it is proposed that "selective cell death within each tumor ecosystem may be one mechanism that induces cancer cell heterogeneity thus confers a survival advantage on these cells". In support to their proposition, the authors claim that there is an association between the apoptotic index in a selection of tumor types and the cancer cell diversity estimated on the basis of transcriptome analysis and patients' survival.

Although the correlation between the increased cell turnover and the aggressiveness of a tumor could be interesting, the authors miss the opportunity to propose a more coherent systemic explanation based on such a solid theoretical foundation as the Darwinian Theory. The superficial analogy with the natural ecosystems may give the illusion that the authors incorporate a Darwinian logic in their explanatory scheme. This is clearly not the case. Their proposition that apoptotic cells purposefully "induce" heterogeneity in the cancer cell population to promote the survival of the fittest sub-clones in the tumor is at odd with any Darwinian logic. Rather, this appears as a simple deterministic reasoning seeking linear causality behind complex phenomena. Such an idea might be compelling but, unfortunately, is misleading. Indeed, this interpretation is regrettably common in biology and it represents a major hindrance for the development of a coherent theory of living organisms (Soto *et al.* 2016).

References

Bizzarri, M, Masiello, MG, Giuliani, A, & Cucina, A 2018, "Gravity constraints drive biological systems toward specific organization patterns: Commitment of cell specification is constrained by physical cues", *Bioessays*, vol. 40, no. 1, doi: 10.1002/bies.201700138.

Brock, A, Chang, H, & Huang S 2009, "Non-genetic heterogeneity—A mutation-independent driving force for the somatic evolution of tumours", *Nature Reviews Genetics*, vol. 10, pp. 336–342, doi:10.1038/nrg2556.

Khatib, S, Pomyen, Y, Dang, H, & Wang, XW 2020, "Understanding the cause and consequence of tumor heterogeneity", *Trends in Cancer*, vol. 6, no. 4, pp. 267–271, doi: 10.1016/j.trecan.2020.01.010.

Kupiec, JJ 1997, "A Darwinian theory for the origin of cellular differentiation", *Molecular and General Genetics MGG*, no. 255, pp. 201–208, doi: 10.1007/s004380050490.

Kupiec, JJ 2020, "A probabilist theory for cell differentiation, embryonic mortality and DNA C-value paradox", *Organisms. Journal of Biological Sciences*, vol. 4, no. 1, pp. 80–85. doi: 10.13133/2532-5876/16955.

Montévil, M, Mossio, M, Pocheville, A, & Longo G 2016, "Theoretical principles for biology: Variation", *Progress in Biophysics and Molecular Biology*, vol. 122, no. 1, pp. 36-50. doi: 10.1016/j.pbiomolbio.2016.08.005.

Paldi, A 2020, "Stochastic or deterministic? That is the question", *Organisms. Journal of Biological Sciences*, vol. 4, no. 1, pp. 77–79, doi: 10.13133/2532-5876/16963.

Sonnenschein, C, & Soto, A 2021, "Control of cell proliferation: Is the default state of cells quiescence or proliferation?" *Organisms. Journal of Biological Sciences*, vol. 5, no. 1, pp. 33–42, doi.org/10.13133/2532-5876/17338.

Sonnenschein, C, & Soto, AM 2020, "Over a century of cancer research: Inconvenient truths and promising leads", *PLoS Biol*, vol. 18, no. 4, e3000670.

Soto, AM, Longo, G, & Noble D (eds.) 2016, *From the century of the genome to the century of the organism: New theoretical approaches. Special issue. Progress in Biophysics and Molecular Biology*, vol. 122, no. 1, pp. 1–82.