Review of: "Introduction to Evolutionary Cancer Cell Biology (ECCB) and Ancestral Cancer Genomics"

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His manuscript undoubtedly represents an effort towards recording a collection of research articles on topics related to the atavistic theory of cancer, introduced by Davies and Lineweaver (Davies & Lineweaver, Physiological Biol 2011, more recently Lineweaver and Davies, Ch.12, pp. 243-261 in The Physics of Cancer, Bernhard S. Gerstmann, Ed., World Scientific, Singapore, 2020), who themselves refer to (Israel J Theor Biol 1996). It provides the main ideas about the main results of the last years on cancer and cancer-related altered genes as failures of control of multicellularity, reversal to overexpression of genes of unicellularity with respect to genes of multicellularity, etc., as tracked by Domazet-Loso & Tautz (for phylostratigraphic analyses) and Trigos et al. in David Goode's lab (for paleogenomic studies), cited by the author.

However, this manuscript suffers, to my eyes, from a main flaw, as it is unfortunately too cell-centred, i.e., not taking enough into account the peritumoral environment; in particular, Soto & Sonnenschein's TOFT is ignored. Secondly, plasticity, i.e., gain of differentiation potential in cancer cell populations, is not considered, whereas reasonably enough, authors, as recorded in Ch. 1 of Marta Bertolaso's Philosophy of Cancer (Springer 2016), have pointed out that cancer is basically a failure of control on cell differentiations. Likely, the author's cell-centred viewpoint explains this non-consideration. Indeed, the genes of multicellularity that are altered in cancer have a fundamental role in maintaining the cohesion of any multicellular animal anatomy and physiology; in other words, its body plan (as a programme of development and maintenance) fails locally to ensure this maintenance in cancer. The 'locally' is not to be neglected, as cancer is always initially the cancer of an organ, which is often not enough underlined.

This way, the author misses, to my eyes, an important point: the cancer-related altered genes result locally (in the tissue or organ concerned by cancer) in uncontrolled plasticity, unchaining capacities that are present in every nucleated cell (as the atavistic theory states), and have been necessary to guide the succession of differentiations that have led to the organism from the initial cell, the zygote, but must be more and more chained as development goes on, to be revived physiologically in very controlled situations, such as tissue repair (wound healing and the axolotl), lest the cohesion of the organism fails, which is indeed what cancer is about (note Thomas Pradeu's motto: 'Cancer is a deunification of the individual.' in Pradeu, Philosophy of Immunology 2019). Such functional consequences of the alteration of the genes of multicellularity related to cancer should be presented in the present manuscript if it is to be a more complete review of the mechanisms that lead to cancer from such alterations, and this should be performed in a tissue-centred perspective.