

Review of: "Somatic evolution of Cancer: A new synthesis"

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This is a rather well-documented review of articles on tumorigenesis, that aims at presenting cancer as taking its origin in ill-controlled mechanisms of wound healing in adult animals. This is totally correct from my point of view, and I equally totally share the viewpoint of the authors about cancer being an uncontrolled revival of ancient somatic mechanisms. What is not clear in their text is that all such mechanisms are linked to control of differentiation, at least as much as to control of proliferation. See on that point Marta Bertolaso's *Philosophy of cancer*, Springer 2016. Indeed, to my eyes, cancer is, at least not initially, a matter of chained stochastic mutations, as unfortunately a widespread biological opinion on oncogenesis puts it, but rather a matter of loss of control on local differentiations, coming from a defective cellular environment. From this point of view, I have noted a number of improvements between the two versions, v1 and v2, of the text I have read, and I am happy to note that the authors document their views more and more widely. Firstly, the atavistic theory of cancer (first presented in Davies & Lineweaver *Phys Biol* 2011, although emerging ideas on it occurred earlier, such as in Israel J *Theor Biol* 1996) is not ignored. By the way, in general, I encourage the authors to not only cite the last papers published on a theory (any theory) that is gradually taking shape, but also to cite princeps articles. Another point, obviously to link to the first one, is the (partial?) understanding that cancer is a disease of multicellular animals only. This idea induces any researcher not only focusing on cell-centred investigations (intracellular signalling pathways, etc.) to ask the question of how such multicellularity is so cohesive, consisting of so many cell types (admittedly about 200 in Humans, 20 in sponges *Porifera*, according to Werner Müller *Int Rev Cytol* vol. 235, 2004) that physiologically and anatomically are compatible and cooperative, and to set the question of phenotype (not genetic) plasticity in cells and of its adaptations to changing cell environments in cell populations. Such plasticity is obviously controlled in a totally mastered way in embryogenesis (and more generally in ontogenesis), following a body plan (*Bauplan* for W. Müller) specific of each animal species, from the single cell zygote, reproducing the same genome in all cells, with different phenotypes corresponding to epigenetic expression or silencing of genes, eventually leading to an adult animal constituted of terminally differentiated cell types. Plasticity is the opposite of full differentiation, it might be defined as a potential of phenotype expression. It must be strictly controlled by mechanisms (likely linked to a whole-organism set of acellular regulations acting on intracellular gene regulatory networks... still to be discovered, although Eric Davidson and colleagues have opened a way in this direction) that ensure that differentiation is irreversible in the process of ontogenesis of each body plan - although we know that by artificial manipulation of Oct3/4, Sox2, KLF4 and c-Myc genes, Shinya Yamanaka has shown, as reported in *Cell* 2006, that such phenotype reversion is in principle always reversible (no wonder, cell differentiation is not a matter of mutations, but of epigenetic modifications, in the genome). The idea, proposed by the authors of the present text under review, that oncogenesis is a way of uncontrolled stimulation of wound healing and tissue repair, is right, however it

should be stated that it is a lack of control of cell plasticity (or of cell differentiations), a control process that is normally irreversibly performed in animal development, producing the physiologically necessary different cell types of an animal organism, and closed at adult age with the necessary exception of wound healing and tissue repair. Indeed, investigating in detail the mechanisms responsible for reversal of plasticity in terminated wound healing should be a royal way in understanding control of cell differentiations and how it is impaired in cancer. I would like to add something about the atavistic theory of cancer: I am not at all convinced of the existence of a Metazoa 1.0 plan that cancer would recapitulate. The only atavistic programme to my eyes is the body plan of each species (a plan is nothing else than a program, and this one, physiological and anatomical, is contained in the zygote, possibly not only in its DNA), which is initially locally in its anatomy impaired by some cell environment-like mechanism in cancer. Going back to the text proposed by the authors, I would suggest that they investigate in detail in the scientific literature on cancer plasticity and its control in cell differentiations, and animal multicellularity in an evo-devo perspective, possibly enriching their views by the consideration of a physiological and anatomical body plan - which incidentally I consider as the evolutionary unit (a programme) the evolution of species applies to.