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

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In a few recent years, Vladimir F. Niculescu (VFN) agitated the scientific community by a series of articles on the origin of cancer. In view of the generally evident failure in treatment of cancer, particularly metastatic, likely stemming in its poorly understood nature, these attempts as a platform for discussions are justified and even needed. The current paper of VFN entitled “Introduction to Evolutionary Cancer Cell Biology (ECCB) and Ancestral Cancer Genomics”[1] reflects the general consensus that cancer has a very ancient origin in the beginnings of the Life on Earth. Two main positions are put forward: (1) Evolutionary Cancer Cell Biology (ECCB) ... reveals that the cancer genome evolved ... long before...metazoans and humans emerged, moreover, it appeared already in the common ancestor of amoebozoans, metazoans, and fungi which has a deep homology with cancer**;** (2) ECCB postulates that somatic mutations are only secondary, downstream events in the process of oncogenesis. In my view, these positions may be currently both supported and opposed or at least, reconciled and completed from the latest literature.

VFN backs the concept of ECCB by the seminal phylostratigraphic studies of cancer transcriptomes and the origin of cancer driver genes in the works by Domazet-Lošo and Tautz [2] and Trigos et al.[3]. Quite similarly, both revealed that a significant number of protein domains associated with cancer “have origins in unicellular organisms (*UC genes*) and both authors also identified a second wave of cancer drivers emerged in early multicellular animals (*MC genes*) of Eumetazoa and Metazoa.

However, in the latter evolutionary strata, division for somatic and germ cells and embryo proper evolved. The early embryo of the primitive green algae Volvox carteri had already the same pattern as a human embryo [4] with one exception – the blastomeres are linked by cytoplasmic bridges, so the Volvox embryo represents, in fact, a polyploid cell. Just by this detail, it is so similar to polyploid giant cancer cells (PGCC) postulated by Niu et al [5] as the dedifferentiated into blastomere-like cancer stem cells; this reference was missed by VFN. For reconciliation, it is very important, in my view, to convey two points: (1) Cancer genome is shifting gene expression to the unicellular pattern linked to cancer by polyploidy [6] as also mentioned and cited by VFN and (2) the emergence of early multicellulars had a very prolonged evolutionary history converting haploid cells into endopolyploidy cells, splitting them back into individual unicellular organisms (also spores) by cellularization, gathering them into transient colonies of the radially-set individuals and so on – the evolutionary laboratory of Protists [7] worked out the whole kit of stress adaptation tools in unstable Metazoa 1, as formulated by Davies and Lineweaver [8]. It is tempting to suggest that the radial pattern of the blastomeres in the early embryo and embryogenesis as such originated from these radial unicellular colonies created in hostile environments. Are

somatic mutations only secondary in this case? If we look attentively at the Gene cards of 12 core genes of Unicellular origin, found by Trigos et al. [3] as a the mostly densely interacting Unicellular cancer-associated network core in a human genome - RCC2, TLN1, VASP, ACTG1, PLEC, CTTN, DSP, ILK, PKN, CTNNA1, CTNND1, PKP3 – we realise that they all characterise the setting, arrangement and remodelling of actin filaments of the mobile cytoskeleton. Thus, it really can be characterised as a phenotypic amoeboid feature, even as a final default state of EMT towards metastatic ameboid transition known for very aggressive cancers [9]. Moreover, we and others described the amoeboid polyploidy, including encystation and excystation of some PGCCs in cell lines resistant to treatments [10][11]. In the latter work, the role of the invasive Rho-GTP-ase Cdc42-kinase in PGCCs malignancy was shown, while this protein binding is needed for the activity of the above mentioned PKN protein of the actin-modulating Trigos's set [3]. Interestingly, in the very useful scheme by Trigos et al. [3] on Fig.S14 demonstrating evolutionary GOslims, a cytoskeleton organisation is located in the period of transition of unicellulars to multicellulars. In turn, the embryo development is at the beginning of multicellularity.

On the other hand, in the capital review on the oncogenes by Janis Erenpreiss[12] published 30 years ago, he showed that what is now called cancer drivers were represented by the proto-oncogenes indispensable for germ cell development. Among them, c-kit, c-fos, c-jun, K-ras and H-ras are involved in the prophase of male meiosis, c-myc – in female meiotic prophase, while ras-family proto-oncogenes are acting through the oocyte maturation, ovulation and embryo cleavage. Moreover, overexpressed oncogenic ras (and we know now that it can be overexpressed by the stress-induced senescence [13]) can cause mito-meiotic transition in somatic cells through insulin-induced oocyte maturation pathway[12]. Clearly, speaking about cancer germline features, the asexual, parthenogenetic-like cancer traits are presumed [12][14]. The proto-oncogenes in this case, may be activated either epigenetically, or by a typical mutation (ras), or by amplification (c-myc). So, in this case, we cannot separate the proto-oncogene overexpression, also by primary mutations from the epigenetic cell changes transforming normal cells into cancer by cryptic evolutionary programs. Not only upregulation of cancer drivers related to oogenesis and embryogenesis was shown on cancer patient material from TCGA database [15] but such early-embryo-mimicking cells were found and demonstrated, for example in male melanoma, treated with vemurafenib – as 4-8-nuclear OCT4-positive PGCCs surrounded by zona-pellucida [16]. Finally, we also have to consider the Euteleostomi phylostratum of the Cambrian explosion (only ~ 500 mya) and even much recent acquisitions of the gametogenesis-associated traits of metastatic cancers through cancer-testis-associated genes amplified in mammals and further in hominids, as well the evolutionary very recent (50-27 mya) domestication of ERV viruses contributing in tumour invasion, both are still evolving. They are evolving together with cancer, unfortunately accelerating its frequency in the 21st century [16]. Thus the stress-adaptive evolution of cancer stemmed from transition of unicellular to multicellular organisms is expanding in human genome to now-days evolution with its environment pollution and climate-change stress and should be further viewed in a wider context, needing more studies.

References

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