Progress in Biophysics and Molecular Biology 122 (2016) 70–76

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Carcinogenesis explained within the context of a theory of organisms

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ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form
28 July 2016
Accepted 29 July 2016
Available online 3 August 2016

Keywords:
Tissue organization field theory
Default state
Closure
Organicism
Stroma epithelium interactions

ABSTRACT

For a century, the somatic mutation theory (SMT) has been the prevalent theory to explain carcinogenesis. According to the SMT, cancer is a cellular problem, and thus, the level of organization where it should be studied is the cellular level. Additionally, the SMT proposes that cancer is a problem of the control of cell proliferation and assumes that proliferative *quiescence* is the default state of cells in metazoa. In 1999, a competing theory, the tissue organization field theory (TOFT), was proposed. In contraposition to the SMT, the TOFT posits that cancer is a tissue-based disease whereby carcinogens (directly) and mutations in the germ-line (indirectly) alter the normal interactions between the diverse components of an organ, such as the stroma and its adjacent epithelium. The TOFT explicitly acknowledges that the default state of all cells is *proliferation with variation and motility*. When taking into consideration the principle of organization, we posit that carcinogenesis can be explained as a relational problem whereby release of the constraints created by cell interactions and the physical forces generated by cellular agency lead cells within a tissue to regain their default state of *proliferation with variation and motility*. Within this perspective, what matters both in morphogenesis and carcinogenesis is not only molecules, but also biophysical forces generated by cells and tissues. Herein, we describe how the principles for a theory of organisms apply to the TOFT and thus to the study of carcinogenesis.

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http://dx.doi.org/10.1016/j.pbiomolbio.2016.07.004
0079-6107/

"Theories never proceed from facts. Theories only proceed from previous theories, often very old ones."

Georges Canguilhem, Knowledge of Life

"The human mind delights in finding pattern—so much so that we often mistake coincidence or forced analogy for profound meaning. No other habit of thought lies so deeply within the soul of a small creature trying to make sense of a complex world not constructed for it."

Stephen Jay Gould, The Flamingo's Smile: Reflections in Natural History

1. Introduction

Since Aristotle, living objects were referred to in terms of teleology and circular causality. These properties of the living were further addressed by Kant in the 18th century, and were successfully adopted by the teleomechanists as a proper heuristic for the understanding of biological phenomena. This causal circularity and interdependence between the organism and its parts was clearly different from the reductionist perspective of Newtonian mechanics. Since then, and before the term "organicism" was created, this organicist view was adopted by an increasing number of biologists. By the mid-19th century, encouraged by the early success of organic chemistry elucidating some aspects of digestion and nutrition, there were biologists who opted for a reductionistic perspective. However, research in biology was then centered on the organism, its development and plasticity, exemplified by the discovery of polyphenism and environmental determination of phenotypes. This is the tradition to which belonged the pathologists who studying cancer in the last half of the 19th century considered this disease to be a problem of defective tissue architecture.

The early 20th century is marked by what Lenny Moss called the "phylogenetic turn", that is, the passage from the idea that the agency for the acquisition of adapted form resides in the organism and its ontogeny, to the idea that it should be sought in phylogeny. The agency thus relocates in an external force, natural selection. "As the genetic program moved to the explanatory center stage, the individual organism, with its own adaptive capacities, began to recede from view." (Moss, 2003). The re-discovery of Mendelian genetics and the introduction of Darwinism are linked to this change; admittedly, the reductionism brought about by the phylogenetic turn reached its zenith with the dominance of the modern synthesis. This early-20th century perspective shifted the attention from organisms to cells, as reflected by the introduction of cell-tissue culture techniques, and most particularly, genetics. This theoretical shift affected all biological fields, including cancer.

For over the last one hundred years, cancer has occupied a privileged position among the diverse diseases that have plagued humans by virtue of its perceived uniqueness. In the first five decades of the last century, cancer and infectious diseases shared the special attention of physicians and biologists, as well as that of the public at large. However, with the advent of effective antibiotics against bacterial infections and tuberculosis (penicillin and streptomycin, respectively), cancer became the center of attention for a significant portion of the biomedical community. By midcentury, two main competing cancer theories were already being proposed to explain the disease. They were addressing the cancer problem at different levels of organization: one regarded cancer as a cell-based disease (centering mostly on the control of cell proliferation), while the other regarded cancer as a tissue-based disease (focusing on altered morphogenesis).

The cell-based theory is known as the somatic mutation theory (SMT); its paternity is assigned to Theodor Boveri who, in his original 1914 German-language version of his book, proposed that at its core the cancer problem was located inside the nucleus of a normal cell that acquired changes in its chromatin that somehow would convert it into a cancer cell. Boveri insightfully maintained that it was impossible to observe the cancer process at what he called *statu nascendi*: this truism is still valid today. Soon after, the development of a tumor mass was attributed to mutations in this cancer cell that made it proliferate autonomously skipping organismal control (Boveri, 1914, 1929; Triolo, 1964). Ever since, the main premise of the SMT has been that cancer is a cell-based disease and implicitly, it acknowledged that the default state of cells in multicellular organisms was *quiescence*.

Theodor Boveri's original version of the SMT represented a significant departure from the viewpoint dominant in the late 19th century among German pathologists who considered that cancer was a tissue-based disease (Triolo, 1964). In 1936, Conrad Waddington and John Needham briefly elaborated on this tissue-based perspective and posited that cancer was, instead, a process akin to abnormal development (Waddington, 1935; Needham, 1936). This tissue-based alternative to the SMT remained as a minority view on the subject and did not receive much support until later in the 20th century.

Soon after the midcentury, and more specifically, after the momentous discoveries that followed what is dubbed as the Molecular Biology Revolution, the SMT attracted the focused attention of the cancer research community. This gigantic research program adopted a reductionist strategy that followed the original SMT premise, i.e. cancer is a cell- and gene-based, molecular disease. Early warnings regarding this interpretation of data were dismissed or ignored, and research proceeded, and still does, under those epistemological arguments. Among early skeptics, David W. Smithers published an impassionate critique in 1962 which maintains its relevance in the present day; entitled "An attack on cytologism;" it exposed the shortcomings of the SMT and proposed, instead, that cancer is a problem of tissue organization (Smithers, 1962). Today, even the most ardent backers of the SMT and the War on Cancer effort have acknowledged that the promised explanations of cancer and its eventual cure have not materialized (Weinberg, 2014; Hanahan, 2014; Sonnenschein and Soto, 2013).

After having spent almost three decades working on the control of cell proliferation in multicellular organisms, in 1999, we proposed an alternative theory of carcinogenesis that we called the tissue organization field theory (TOFT) (Sonnenschein and Soto, 1999). Ever since, our theory has challenged the hegemony of the SMT to explain cancer while adopting an organicist perspective; in this context, our attention was focused on the level of biological organization at which the subject of inquiry, cancer, is being observed, namely, the tissue level and thus, as a problem of tissue organization akin to histogenesis and organogenesis (Sonnenschein and Soto, 2008; Soto and Sonnenschein, 2011). From our perspective, carcinogenesis is a process analogous to embryonic development, whereby organs are constructed through interactions among different cell types; in short, this means that cancer is a relational problem (see below). Equally important, if not of greater impact in biology at large, we explicitly incorporated into the TOFT the basic premise that *proliferation with variation and motility* is the default state of *all* cells. The implications of adopting this premise have been highlighted in separate articles of this issue (Longo & Soto, 2016; Soto et al., 2016; Montévil et al., 2016b).

2. Basic notions about cancer as a human disease

Before considering the relationship between the TOFT and the theory of organisms, a brief account of the general subject of cancer