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One hundred years of somatic mutation theory of carcinogenesis: Is it time to switch?

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Cancer theories in their historical context

During this current year of 2014 biologists and cancer researchers will commemorate the centenary of the publication of *Zur Frage der Entstehung maligner Tumoren* (*On the Origin of Malignant Tumors, Williams & Wilkins. Philadelphia, PA, USA)* by the German zoologist Theodor Boveri, a book that directly and indirectly impacted both the biological sciences at large and cancer research in particular. Before 1914, Boveri made important contributions in the fields of Mendelian inheritance, cellular and developmental biology: among others, the Sutton–Boveri theory of chromosomal inheritance; the individuality of chromosomes and the concept that the *assortment* of chromosomes rather than their *number* was necessary for development; the finding that comparable sets of chromosomes are contributed by the oocyte and the sperm. Boveri also paved the way for the discovery of the "organizer" by Spemann and Mangold [1]. These contributions were the fruit of his great observational skills, experimental ingenuity and dexterity, and his theorizing acuity. Finally, he wrote the aforementioned book, widely acknowledged to be seminal in cancer pathogenesis.

From the end of the 18th century to the 1840s, great advances in morphology, physiology, and embryology took place in Germany due to the methodological insights introduced by the philosopher Immanuel Kant and the biologist Johannes Friedrich Blumenbach. The study of the organism was then guided by what today is called an organicist perspective, whereby no body part could be understood but in relation to the other parts and the whole itself [2]. The birth of experimental embryology (1890s), the rediscovery of Mendel's experiments (ca. 1900), the birth of genetics (ca. 1911, if one accepts Morgan's conversion as the starting point) and of cell culture (1907–1912) ushered in a more reductionist view in biology, culminating with Boveri's claim that embryology will become a biochemical science [1].

In the Introduction of his book, Boveri expressed his misgivings about proposing his theory on carcinogenesis, given the cold reception he sensed when he first exposed it among his colleagues. The first English translation only appeared in 1929 (by Boveri's wife, Marcella)[1]. Shortly after Boveri's death in 1915, Whitman introduced the notion that the

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cancer cell was a "mutated" cell, and coined the idea of a somatic mutation to explain what Boveri had implied in his 1914 narrative (for further details, see [3]).

In his book, Boveri makes two main claims: the first is that *proliferation* is the default state of cells ("I hold it to be without any doubt that the tendency to continued multiplication is a primordial quality of cells, which only becomes inhibited in many-celled organisms through environmental influences." pages 113–114 and 26–27). In truth, this concept was originally stated by German pathologists in the 1880s. Boveri and his predecessors merely seem to have accepted this concept as a self-evident truism. In the mid-20th century, microbiologists also made explicit that proliferation was the default state of unicellular organisms. F. C. Steward, a botanist, shared this view with regard to plant cells [4].

In the 1980s, we reported experimental evidence supporting the notion that the default state of metazoan cells was proliferation, and extended this concept to encompass *all* cells [5]. After all, life could not have arisen and propagated unless proliferation were a constitutive property of cells, thus spelling out the evolutionary relevance of this concept. In *On The Origin of Species* (1859), Charles Darwin explicitly stated the concept of reproduction followed a geometrical progression when he wrote "…There is no exception to the rule that every organic being naturally increases at so high a rate, that, if not destroyed, the earth would soon be covered by the progeny of a single pair." Thus, it appears counterintuitive that the concept of proliferation as the default state of *all* cells is not mainstream today.

Boveri contradicts himself when claiming that not only are there "inhibiting chromosomes" (his quotation marks) but also "chromosomes which *promote* division" (his quotation and italics; pages 26–31). Boveri seems to have conflated the need to execute the proliferative process (in today's terms, the cell cycle, answering the question: *how* does a cell proliferate?), and the need to regulate the entry of the cell into the cycle (answering the question: *why* does a cell proliferate?). Admittedly, Boveri's writings preceded by several decades the discovery of the cell cycle.

The second important message of Boveri's book is that cancer is a *cell-based* disease. Unambiguously, he writes "…*the problem of tumors is a cell problem*" (Boveri's italics) (pages 3, 40, 78). This claim contains two subordinated claims, namely (a) that cancer is a problem of cell proliferation and (b) that cancers are due to an abnormal chromosomal rearrangement ("…cancer is due to a chromosomal rearrangement that eliminates a portion of chromosomal material whose function is to inhibit cell proliferation" pages 26–27, 43–51, 90). Again quoting Boveri, "…in these altered conditions, the [tumor] cell reacts differently to its surroundings and this might be the sole cause of the tendency to unchecked cell multiplication" (page 6). Finally, Boveri made the distinction that it is not abnormal mitosis that is the cause of cancer, but abnormal chromatin-complex ("…the essence of my theory is not the abnormal mitoses but a *certain abnormal chromatin-complex, no matter how it*

[1]An annotated translation of Boveri's book into English by Sir Henry Harris, Regius Professor of Medicine Emeritus at Oxford University under the title Concerning the Origin of Malignant Tumors has recently been published (2007). In it, Sir Henry dismisses the notion that cancer is a *tissue-based* disease. Instead, he favors a *cell-based* explanation whereby a causal role of carcinogenesis is attributed to DNA mutations in so-called oncogenes and suppressor genes that would not directly affect cell proliferation but cell differentiation.

arises." – Boveri's italics, page 34). For a century now, this concept has been kept at the center of the somatic mutation theory (SMT).

Boveri's original SMT was subject to modifications during its centennial course. The current SMT retains the premise that cancer is a *cell-based* disease in which DNA mutations affect the control of cell proliferation. Against Boveri's conviction, the current SMT switches the default state of cells from *proliferation* to *quiescence*. This misper-ception facilitated the introduction of "stimulators" of cell proliferation in the form of "growth factors" and "oncogenes", entities that, on the one hand, lack a biological reality and, on the other, unwittingly introduced a type of creationism into biology [4] [2]. It is remarkable that the significant switch in the nature of the default state of cells was never made explicit by past or current SMT supporters.

The immediate impact of Boveri's book

As with many other important novel messages in the sciences, Boveri's did not immediately shake the medical or the scientific community. Nevertheless, the geneticists Thomas H. Morgan, Calvin Bridges, and later other members of the Columbia University Drosophila group, aligned themselves with Boveri's idea of the SMT. Meanwhile, some biologists objected to Boveri's claim about the centrality of the "cancer cell" in carcinogenesis. In the 1930s, for instance, Conrad Waddington revived the notion that cancer was instead a disease of development, consistently presenting a concept that was compatible with the assumption that this was a *tissue-based* disease; later, J. W. Orr's experimental work buttressed this notion. As late as 1962, David W. Smithers passionately proposed abandoning the cytologism of Boveri's ideas and replacing it with an organicist view on the *tissue-based* quality of cancers [4]. These criticisms were, however, ineffective in switching reductionist views that prevailed throughout the 20th century.

The current impact of Boveri's theory

A more optimistic, although somewhat mischievous, interpretation of the significance of Boveri's book on biology at large, and of carcinogenesis in particular, was made indirectly by John Cairns, who wrote in 1997 "…Although study of the molecular biology of cancer has not yet laid bare the causes of most cancers or produced a cure, it has enormously increased our understanding of the molecular biology of the mammalian cells" [6]. Indeed, the spectacular explosion of powerful molecular biology techniques made possible the accurate tracking of thousands of somatic mutations in cells from tumors, now known also to be present in normal cells of normal hosts. This latter, unexpected, finding complicates even more the search for those still elusive cancer "driver" mutations [7]. Be that as it may, Boveri's original speculation ("I am convinced that every theory of malignant tumors is wrong which does not take into account its unicellular origin." page 40) remains the central tenet of the current version of the SMT [8].

Most of Boveri's current followers consider that mutations in the cell cycle components affect the speed at which the original tumor cell and its descendants proliferate; however,

[2]If the default state is *quiescence*, what or who induced the proliferation of the first ever cell(s) at the beginning of life?

there is no experimental evidence supporting the generality of that claim [8]. Moreover, looked at from the cell-level perspective of biological organization, those genomic alterations have not changed the fact that, as with normal "mother" cells, cancer "mother" cells also generate two similar "daughter" cells. Thus, the chromatin complex aberrations (i.e. mutations) that Boveri and his followers have alluded to since 1914 may have either a "neutral" effect on somatic target cells, or they are just a *consequence* of the carcinogenic process rather than its ultimate cause [5].

Additionally, as gleaned from textbooks on genetics, there is a consensus that genomic mutations in a normal ("wild" type) cell are either deleterious or neutral to the cell's viability. Nevertheless, when dealing with carcinogenesis, Boveri and his followers consider plausible the intriguing notion that a single mutated somatic cell (or one carrying genomic and/or chromosomal aberrations) acquires an enhanced capability to proliferate autonomously, and that eventually the continued proliferation of such a single, somatic, mutated cell kills the host in which it has originated. In this particular regard, technologies based on the SMT have generated a body of data that seriously challenge the worthiness of this speculation. For instance, using diverse experimental models, researchers have shown that mutated somatic cells (including carriers of chromosomal aberrations) belonging to cancers can be "normalized" [5]. This compelling evidence against the SMT is either ignored, or else incorporated as "add-ons" to the SMT in which the microenvironment also plays a role in carcinogenesis – albeit always subservient to mutations [8].

Returning to the impact of Boveri's book, the verdict on the SMT is now fairly clear. Despite the spectacular technological advances in the fields of genetics, and in cell and molecular biology, (i) the SMT has been aggressively explored but, so far, not tested experimentally [5]; (ii) the SMT-inspired collected evidence tends to rule out the notion that cancer is a *cell-based* disease; and (iii) the success of therapies based on the SMT, are acknowledged, even by their supporters, to be meager to non-existing [9].

The regrettable irony remains that Boveri's sensible and evolutionarily relevant premise that *proliferation* is the default state of *all* cells was not adopted, whereas his flawed speculative suggestion that cancer is a *cell-based* disease has enjoyed enthusiastic support among cancer researchers to the current day.

Time to move on

Boveri's book centered on two fundamental, interrelated accounts, namely: control of cell proliferation (*proliferation* as the default state of cells) and carcinogenesis (chromosomal aberrations/mutations) as the cause of cancer. The first concept has been practically ignored by the academic community, which has adopted instead the evolutionarily erroneous premise that *quiescence* is the default state of cells in multi-celled organisms. Regarding carcinogenesis, Boveri served as an intellectual inspiration for researchers who, after a century of industrious, expensive efforts, acknowledge that the goal of explaining cancer through the SMT remains elusive [10]. Thus, despite Boveri's previous important scientific personal achievements, perhaps it is time to relegate *On the Origin of Malignant Tumors* to the "historical curiosities" shelf of biomedical libraries. A monumental challenge now

awaits experimental biologists, cancer researchers, and teachers at all levels of instruction. The task is to go back to the metaphoric drawing board and rethink carcinogenesis and biology in general under consistently reliable, evolutionarily sound premises.

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