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Commentary: How Evolution of Quorum Sensing Must Fit into the Understanding of The Origin, Prevention and Treatment of cancer

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"By postulating that gene expression is intrinsically probabilistic and that stabilization of gene expression arises by cellular interactions in "morphogenetic fields", development and cellular differentiation can be rethought in an evolutionary perspective. In particular, this article proposes that disruptions of cellular interactions are the initial source of abnormal gene expression in cancer cells.". Jean-Pascal Capp[1]

Introduction

In my article: "Evolution of Microbial Quorum Sensing to Human Global Quorum Sensing: An Insight into How Gap Junctional Intercellular Communication Might Be Linked to the Global Metabolic Disease Crisis" [2], I attempted to integrate how the original single cell organism, living in an hostile environment, acquired genes to deal with an environment with no oxygen and a need to adapt to changing amounts of nutrients for individual life and the reproductive survival of its species. Its metabolic processes required genes that coded for enzymes needed to metabolize glucose, in the absence of oxygen, to produce energy from an inefficient process to make a couple ATP molecules (anaerobic glycolysis). In addition, to meet the demand that as a single cell, it had to acquire genes to be able to communicate with each other concerning the availability of nutrients. Without that ability to communicate with each other about the status of that nutrient pool, each cell would not change its individual need to consume the nutrients at the "normal" rate. It was the primordial means to communicate that emerged, namely the production of a secreted molecule that could be detected by other members of this population when the nutrient levels are being depleted that would signal all of them to slow down their metabolism. The concept of "quorum sensing" was created to depict this process[3]. If that means of communicating never occurred, the chances of both individual and species survival would be small.

It was during my thoughts of this phenomenon that I recalled Barry Commoner's, The Closing Circle: Nature, Man and Technology[4], which was commented on by my late former mentor, Dr. Van R. Potter[5]. It was here that he (being a famous cancer biochemist and former President of the American Association of Cancer Researchers), stated that cancer cells reminded him as bacteria that no longer communicated with each other. This idea has been later acknowledged[6]. In addition, he reminded me that both the single

cell bacterium and the cancer cell seemed to metabolize glucose in a similar fashion, namely via the Warburg process[7,8]. It was this discussion with Dr. Potter in 1972 that changed my whole approach to thinking about human carcinogenesis, both from a basic mechanistic perspective and a moral perspective (It has to be noted that Dr. Potter was the person who coined the term, Bioethics" and "Global Bioethics" [9,10]). In fact, his Presidential Address was titled: "Bioethics for Oncologists: A Humility with Responsibility"[11]. Equally important is the idea that one must always view a human medical problem, such as cancer, from an evolutionary perspective ("Nothing makes sense except in the light of evolution"[12]).

While all the historic steps, taken by me and my laboratory from that point on, was, in large part, shaped by scientific discoveries by the whole scientific community, on a personal level, awareness of the magnitude of the global frequency of all cancers was , and is, staggering, as well as the total global "metabolic diseases" . While there are many factors, both biological, ecological, sociological, behavioral and cultural, that have contributed to cancer being a major cause of human suffering and death, the point made is that, while we know much that can contribute to the causes of cancer, our prevention and treatment strategies are less than acceptable.

Most oncologists agree that past cancer treatment strategies have been based on outdated ideas of, not only what a cancer cell is or where it arose, e.g., the "stem cell hypothesis"[13] or a "de-differentiation or Re-programming hypothesis"[14], but the newer experimental basic scientific understanding has yet to be integrated into a new strategy. With early demonstration of the carcinogenic process being described by the "Multi-stage"/ Multi-mechanism" phenomenon[15,16], set off a number of experiments to identify both the stages and underlying mechanisms of each stage. The operational terms of the single normal cell had to be **irreversibly** transformed into an "**initiated**" cell (a cell that was "immortal" and could not terminally differentiate or apoptose)[17]. Recall, it was determined that all cancers originated from a single cell[18,19], while each tumor derived from that single cell contained a mixture of diverse abnormal genotypes and phenotypes. Next, that single initiated cell could be clonally amplified by agents or conditions, that themselves, were not capable of "initiating" a cancer. These agents and conditions were referred to as "**promoters**" or acting via epigenetic mechanisms. These promoting agents seemed to have thresholds, needed to act in the absence of "anti-promoters" or in many cases, by anti-oxidants, and have a long and regular exposure to the initiated cell[20]. This led to the formation of benign lesions, such as a papilloma of the skin; polyp in the colon, nodule in the breast. Finally, when sufficient cell divisions have occurred in these initiated cells, such that a single cell acquired the "hallmarks of cancer"[21,22], a cell had, then, reached the **progression** stage, when it now could invade tissues and to metastasize to other organs.

While the underlying molecular mechanisms for each of these three stages are yet to be universally accepted, **mutagenesis**, an irreversible step, seems to be the basis for converting a normal cell to an "initiated" cell. It has to be made clear that there are at least two different mechanisms of mutating a gene, namely by an "error in DNA repair", as in the case of the skin cancer-prone syndrome of xeroderma pigmentosum[23], or by an "error in DNA replication", as in the case of the cancer-prone Bloom's syndrome[24]. On the other hand, altering the expression of genes at the transcriptional, translational or posttranslational level by **epigenetic mechanisms** seems to explain the promotion process[25], in that, the promotion of an initiated cell can be interrupted or reversed[26].

Normal Cells are like Single Organism Cells, Namely They Can Communicate With Each Other

With the evolutionary appearance of multi-cellularity when the earth became oxygenated, several new cellular phenotypes, with their associated genes, emerged, namely, cell **adhesion molecules** that allowed cells to physically attach to each other to form a cellular close-knit society. The **niche** is designed to create a low oxygen-microenvironment for a new cell type, the stem cell[27]. These **stem** cells also acquired a new means to divide in order to form one stem-like cell as its mother and a cell that could terminally differentiate. These stem cells could either divide **symmetrically** to form two stem-like daughters or **asymmetrically** to form one stem-like daughter and one to terminally differentiate. To make all these new phenotypes to work, homeostatically, to form a higher organism, a new form of cell communication that builds on the single cell organism's means of "quorum sensing", namely **gap junctional intercellular communication (GJIC)**. These multi-cellular metazoan cells retained the secreted form of cell-cell communication via hormones, growth factor and cytokines[28-30], but now had a means to communicate with their contiguous neighbor without having to go through its membrane, cross intercellular space and then into the membrane of its neighbor. It now could transfer ions and small regulatory molecules directly through protein channels[31].

Because it has been shown that there are twenty highly evolutionary conserved genes, the connexin genes, the connexin genes, that exist and are differentially expressed to help specify the differentiation of a cell type. This phenomenon of gap junctional intercellular communication exists between normal somatic cells. While in general, as Loewenstein and Kanno had shown, the ultimate metastatic cancer cell lacked functional GJIC,

the roles of gap junctions during the multi-step, multi-mechanism evolution from the normal cell to the invasive and metastatic cancer cell are complex. During the invasive and metastatic phase the cancer stem cell has been shown in some cases to go through the epithelial-mesenchymal transition to use transient gap junction function for guidance to its ultimate distant organ[33]. This opened up a new way of re-interpreting the "initiation/promotion" hypothesis of carcinogenesis. This happened during the test of a hypothesis that a classic tumor promoter of mouse skin cancers, i.e., phorbol esters, acted by inhibiting DNA repair, thus increasing the mutation frequency[34]. However, in testing that hypothesis, it was shown that phorbol esters did not inhibit DNA repair or act as a mutagen. Instead, it reversibly inhibited gap junctional intercellular communication[35].

One important point needs to be mentioned at this stage that gets to two major issues: (a) the role of which one cell, when, initiated leads to the initiated cell; and (b) where does the role of cell-cell communication play in the promotion process? It turns out that the gap junctions appear at the compaction stage of embryogenesis[36]. Early stem cells and organ-specific adult stem cells do not express or have functional gap junctions[37]. These normal stem cells are kept in their non-differentiated and non-proliferative state by either or both extracellular adhesion molecules or extracellular matrix molecules in their niches and secreted factors from their derived differentiated offspring[38,39]. Once these stem cells are induced to turn off their embryonic genes, such as Oct4, and induced to turn on their gap junction genes, they can now start to differentiate[40].

Therefore, it seemed reasonable to assume that the stem cell, which is naturally "immortal" until it is induced to differentiate or become "mortal", might be the target cell to be initiated. Therefore, the biological consequence of the initiation process is one that blocks the "immortalized" stem cell to terminally differentiate or become "mortal". This interpretation challenges the current paradigm that the first step of carcinogenesis is to "immortalize" a normal "mortal" cell. Furthermore, since it was shown that the "stem cell" was the target cell that led to the "cancer stem cell"[40], it became clear that this normal cell, which has few mitochondria and metabolizes glucose via glycolysis[41,42], once initiated, gave rise to the "cancer stem cells", which gives the tumor the characteristic Warburg metabolic signature. Also, since all tumors are mixtures of both the "cancer stem cells" and partially differentiated ("oncogeny as partially blocked ontogeny"[43]) "cancer non-stem cells", there seems to be sufficient evidence to support the stem cell hypothesis for the origin of cancers.

When Lowenstein and Kanno[31] noted that the cancer cell did not have functional gap junctional intercellular communication, these cancer cells were characterized as having lost "contact –inhibition" or growth control[44], could not terminally differentiate, appeared to be immortalized, and had abnormal ability to apoptose. Normal cells were characterized as having growth control or could "contact inhibit" and could differentiate, and could apoptose and were "mortal". Later, various knockout connexin genes were shown to lead to embryonic lethality[45], whereas when normal connexin genes were genetically engineered into non-GJIC cancer cells, they regain a normal phenotype[46]. On the other hand, using dominant negative connexin genes to be placed into normal GJIC-communicating cells, transformed them to a cancer-like phenotype[47]. Therefore, the connexin genes and gap junctional intercellular communication were associated with growth control, differentiation of stem cells and apoptosis[48].

Evolution of Quorum Sensing in Metazoans: Its Link to Stem Cells and Cancer Stem Cells

If this evolutionary link between a single cell, glycolysis-metabolizing cells, that had vital cell-cell communication by secreted factors that led to quorum- sensing of each other in a loose population, and a multi-cellular metazoan, that added on the gap junctional intercellular communication to produce a society of various new adaptive functions via differentiated cells (eye, muscles, cardiomyocytes, hepatocytes, pancreas, neurons, etc.), had to have growth control via both the secreted factors and gap junctions. If they lost these communication mechanisms, there could be no homeostatic control of growth. In other words, a tumor would be the result.

With the eventual development of consciousness in the brain, a new level of quorum sensing is now raised. It comes back to what Dr. Van R. Potter was referring to when he coined the terms "Bioethics" and "Global Bioethics". While it is important for cancer scientists of all disciplines to get the best basic scientific information available to implement policies for prevention, diagnosis, prognosis and treatment, there is also larger issues, raised by a human global quorum sensing, in that evolution gave us, via the gap junctional intercellular communication, genes that led to making moral decisions.

Cancer is not only a cell problem, it is a human behavioral problem. With our ability to extend human life span by elimination of childhood deaths and elimination of many infectious diseases, we now live longer only to be exposed to the "effluence of our affluence[49]. Over population, environmental pollution of soil, water and air, mal-distribution of wealth, and bad behavior choices contribute to the negative consequences of our cultural evolution. Much of this is the result of our biology that makes us to respond to short term positive and negative effects of our behavioral choices, while not responding to the potential positive and negative long-term consequences

of our choices.

This was the take home lesson of my paper. In early human evolution, we had limited means to communicate with members within our close society, let alone to the distant members of the human society. Today, with each individual and all societies wanting to prevent and treat cancers, the best scientific means to understand the causes of cancer is but one current attempt (e.g., "environmental medicine"; "personalized medicine"; "precision medicine")[50-52]. Even with these new concepts, integration of current scientific knowledge is incomplete[53]. Although it could be argued that our means to have almost instantaneous "quorum sensing" on a global scale, with Twitter, Instagram, Facebook, the internet, and web-based TV, one might communicate that scientific information to prevent, diagnosis, treat cancers on a global scale to make a real dent in the cancer frequency. However, all decisions, that an individual in a pluralistic world makes, have two components: (a) the **factual** or scientific-based information; and (b) the **value** component[54]. It might seem that the scientific or factual component of that decision -making process should not have global barriers. The science of the nature of human carcinogenesis should be identical because there is not a nation-defined fact of this process. Science is universal, not culturally unique. Unfortunately, our values are not universal in a pluralistic world.

However, even in an ideal world that might become more globally connected and more homogenized via the values associated with the individual culture, global human quorum sensing will never be a universal trait, by which each individual would react to the solid scientific information to behave in a manner to prevent or choose a treatment for cancer. In effect, those resisting solid scientific knowledge regarding cancer prevention and treatment will be analogous to the drug-resistant bacterium or a cancer resistant cell.

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