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Tumorigenesis and Its Neovascularization

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Abstract

The hunt and understanding for tumorigenesis is a critical process: its identification might highlight the perspective for the direction of future investigations and could pave the way for the development of new strategies. The article describes a novel hypothesis of an attempt to reevaluate the existing data about human tumorigenesis from the viewpoint of all-epidemiology, pathology, cytology, histological model, genetics and evolutionary discoveries. The new conception in accordance with the status quo will provide a logical framework for understanding tumorigenesis during human ontogenesis and may lead preferentially to breakthroughs and exciting discoveries in the fields of tumor neovascularization.

Introduction

Why and how tumorigenesis occurs during human ontogenesis remains mysterious to the general public and to the medical community. Despite many considerable advances to date, there has not been satisfactory data largely owing to incomplete understanding of tumorigenesis and their biological behavior of this devastating disease. Frustrated and bewildered with the pace of progress in the war against tumor, scientists are still struggling to search for an answer. The purpose of this paper will constitute a logical frame work of the conceptual models that inform medical cancer research by analyzing these discoveries, involving not only recognition of conception and pathogenesis but also implication of potential therapeutic target focusing on the cellular and organic level.

Progress in oncology is closely related to advances in the natural sciences, including biology-especially cytology and genetics-and chemistry-especially biochemistry. During these progresses, a hallmark hypothesis that all solid tumor growth is angiogenesis dependent published in 1971, created the field of tumor angiogenesis [1]. This understanding literally opens a novel way of targeting tumor-associated vasculature. Tumor neovascularization has been closely related to issues of the origin, initial causes, progression as well as pathogenesis of human tumors. However, there is a gap in the understanding of events leading to tumorigenesis and its neovascularization, between conventional concepts and novel ideas.

Historic Background

The oldest description of human tumor (It is called the Edwin Smith Papyrus) was discovered in Ancient Egypt and dates back to about 3000 BC. The Greek physician Hippocrates (460 BC to 370 BC), who is considered the "Father of Medicine", is thought to be the first person to clearly recognize the difference between benign and malignant tumors. His writings include description of cancers involving various body sites. Hippocrates noticed that blood vessels around a malignant tumor looked like the claws of crab. Clearly, human tumors have afflicted throughout recorded history of mankind and did not suddenly start appearing after modernization or industrial revolution.

The 19th century saw the birth of scientific oncology with the discovery and use of the modern microscope [2]. Johannes Peter Müller (1801-1858) and his student Rudolf Virchow (1821-1902), provided the scientific basis for the modern pathologic study of tumor tissues. Since then, it began to be generally accepted that tumor is a disease caused by an abnormal growth of heretical cells, and that all cells, including cancer cells, are derived from other cells. This conception not only allowed a better understanding of human tumor, but also aided the development of tumor pathology and of that pathological diagnosis has become the most reliable basis for tumor until now.

At the turn of the 20th century, the most important advances in oncology were experimental oncology and biochemistry. Scientists attempt to transplant tumors and induce tumors in animals by using a variety of external agents. These studies helped elucidate many characteristics of tumor tissues and cells. In accordance with the types of carcinogens, three basic directions in experimental

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and theoretical oncological research have gradually been established: Viral, chemical, and radiation.

The notion of cancer stem cells (also called tumor-initiating cells) was first introduced in 1994 [3]. Over the last decade, candidate tumorigenic cells have been identified in a variety of human tumors. The theory has ever generated much excitement and optimism within medical world although it is now a subject of debate and still an area of ongoing research [4-6]. Unlike the random model dominant in tumor research, which holds that nearly any cancer cell has the potential to form a tumor, the conception have virtually updated the understanding of tumorigenesis and led to recognize the dynamic nature of cell populations in tumor, with the pluripotent tumorigenic cells harboring ready and able to amass all of the components of a hierarchical organization.

Hunting and Pondering of Tumorigenesis

The epidemiology, as a way to infer possible trends and causes, has been wildly applied to the field of tumors and is now a new branch of oncology-tumor epidemiology. The tumor epidemiology is the study of the factors affecting tumor in order to find the cause of tumor and to identify and develop improved therapies. Epidemiologists continue to search for factors that cause tumor (like tobacco use, obesity, ultraviolet radiation), as well as those things that offer protection against tumor (such as physical activity and a healthy diet). However, unlike the experimental oncology, the epidemiologic research, based mainly on probability, accordingly, must contend with problems of lead time bias and length time bias [7], for example, life-time dilatation, diagnostic level improvement etc. The hundreds of years of experience have shown that tumor epidemiology so far has not screened an inherent cause of any kind of tumor, less exact in many contagious diseases by this method. One possible explanation is that this method may be too macroscopical for tumorigenesis because the object of this method is human (with and without tumor) rather than the tumor itself.

As DNA was discovered to be the basis of the genetic code that gives orders to all cells by the middle of the 20th century, and subsequently was uncovered how to translate this code, scientists can understand how genes worked and how they could be damaged by mutations (changes or mistakes in genes). The genetic hypothesis seems to answer the intricate tumorigenesis that had troubled oncologists for many years [8-10]. One thing we do know about the genetic theory of human cancer cells is that it is impossible to treat. The advance of science and technology carries with it a striking conceptual inconsistency. Although the hereditary substance is the material basis for determining cell fate, which provides the possibilities of a great diversity of diseases at the cellular level, reasoning liking the following insuperable facts and questions drives us to consider: First, all types of human cells including tumor cells are derived from the single fertilized egg cell. In other words, from that point on, all cells of an individual linked by the same the genetic information cells held in common. Second, for past decades, the reported genes, more than 100 oncogenes and 30 tumor suppressor [11], are the basic function genes in the developing or in the adult cells. Third, a phylostratigraphic tracking of oncogenes has suggested a link to the emergence of multicellularity in metazoan which can be traced back to a billion years ago [12]. In other words, almost no new disease associated genes emerged after the evolution of mammals. In addition, A series of recent genetic investigations confronted the somatic mutation theory began to be articulated [11]; scientists doubt whether somatic mutation and selection are really necessary and sufficient to produce the sophisticated survival skills of invading and disseminated tumor cells [13]. Some of them believe the ubiquitous but non-genetic variability can contribute to tumor progression independently of genetic mutations [13]. Taken together, for the specific individual cell, the cytoplasm (including niche) rather than the nucleus holds cell fate and determines the direction of cell differentiation. The successful cloning of Dolly sheep is one of the most famous cases using the technique of somatic cell nuclear transfer because this method becomes possible to derive one kind of specialized cell from another, more accessible, tissue in the same individual [14,15]. More important, as a methodology, it's very difficult for us to search for the carcinogens and to seek any new therapy through the genetic level research of tumor cells because numerous genetic alterations in any tumor are the result, not the cause. Accordingly, at least in the etiology and therapeutics, the genetic level research might be a misleading direction to solve the tumor problem because it may be too microscopical for tumorigenesis.

Virtually, human tumorigenesis is far from the complexity of the origin of life. A cell is the basic unit of life. Today, the diagnosis of human tumors is still cellular hierarchy and organizations abnormalities, for example, benign vascular tumors. As a matter of fact, human ontogenesis is the cellular development process [16]. A cell that possesses advantageous characteristics for survival and proliferation is selected to become the progenitor of a successor cell population that eventually dominates to tumor mass [17]. Recently, some scientists have proponed that tumors are a type of atavism that appears in the adult form when something disrupts the silencing of ancestral genes [18]. Importantly, the growing scientific evidence to support this theory is that one cell of an individual can transform another, for example, induced pluripotent stem cells (especially by non-transfection with genes [19,20]) and Epithelial-mesenchymal transition in tumor [21,22]. Moreover, no two tumors of a given organ in either the animal or the human being would contain tumor cells that are uniformly genetically or phenotypically identical. The above views can well explain the similarity and heterogeneity between tumor and any normal tissues around it. These evidences suggest that cells in a part of the body can dedifferentiate and transdifferentiate into another, consistent with the notion of stem cells (including tumor stem cells), in a way, these differential tumorigenic cells are viewed as those cells at the apex of the tumor hierarchy, which highlights the role of aberrant differentiation for descendants in tumorigenesis. Although not offering an accurate answer to tumorigenesis, we have a better understanding of that tumorigenesis should be focus on the abnormality from the cellular level to the tissue level.

Everyone is at some risk of developing cancer during a normal life span. However, genes or environmental factors alone cannot cause tumor. No doubt, from the beginning of a single fertilized egg cell, it is likely to form tumors, for example, hydatidi form mole. Most tumors begin when normal cells in a part of the body start to transform, evolve, and grow out of control during an individual whole life. For tumorigenesis, we assume the existence of dedifferentiation of the somatic cells in tumor (although they still keep epigenetic memory related to the former cells), similar to the atavism hypothesis of tumor, and the subsequent aberrant differentiation alike to the theory of tumor stem cells. It is reasonable explanation for these appearances: The expression of the related progenitor (or stem) markers and the phonotypical difference of tumor cells within most all tumors. The atavism hypothesis, based

on a link between cancer and the origin of multicellular animals, implied tumors could be the ancestors of multiple cells' animals. Their characteristics are between the animals' single-cells ancestors with duplication along with reckless abandonment, whereas the multicellular animals with restrained replication avoiding adverse effects on organism. Inconsistent with the standpoint, the replications of the body cells become finite proliferation dependent on the degree of their dedifferentiation in face of an environment challenge, and are still between copy of embryonic stem cells and that of normal body cells (self-repairing capability). Further, the atavism hypothesis also indicates that a tumor is the simplest collection or organism of independently evolving cells, which is difficult to explain if all tumor cells act independently, for instance, it will not survive along with the host death. While, our viewpoint is that a tumor is a new organ-like tissue because it is made of multiple cell types and components [4,23]. Recent attention has turned to recognizing interactions of cancer cells with each other as well as other cells in their niche [24]. There are clear examples of cooperation, such as tumor neovascularization, in which one cell type provides a benefit to others [25].

It is very important issue that a tumors is defined as a problem of tissue-based disease [26,27]. For example, a benign vascular tumor presents mainly the structural abnormalities and uncontrolled growth. Current approaches to identifying tumorigenesis came from attempts to transplant putative tumorigenic cells from humans to animals. The barrier to the tumor animal models seems insurmountably because of the niche differences [28], for example, interspecies differences, non matching tissues and immune system, etc. The niche could be linked to identifiable and even preventable causes. A key area of interest lies in learning how to construct a reliable tumor model; regrettably, scientists still could not construct any normal tissue even using normal stem cells until now. This means that we do not know the necessary factors of any normal tissue formation; accordingly, it is very difficult to discover the clues of tumorigenesis, as abnormal tissue.

Understanding of Tumor Neovascularization

For more than 100 years, tumors had been observed to be more vasculars than normal tissues. This phenomenon, which was explained by simple dilation of host existing vessels due to a side effect of metabolites or necrotic tumor products [29], was largely overlooked. Much attention starts from the publication of Folkman's imaginative hypothesis that tumor growth is angiogenesis dependent with regressions of solid tumors to size of ~1 to 2 mm diameter without a blood vessel supply [30], and hence, blocking angiogenesis could be a strategy to arrest tumor growth. The idea has become one of the most exciting and visible areas of cancer research and therapeutics in clinical oncology [31], and led to the discovery of a number of therapies based on blocking neovascularization. According this hypothesis, tumor cells and vascular endothelial cells within a tumor may constitute an integrated ecosystem in common, and endothelial cells may be switched from a resting state to a rapid growth phase by a "diffusible" chemical signal from tumor cells. An additional speculation was that antiangiogenic therapy may be more efficacious for the long term, either alone or in various together with conventional chemotherapy. This is because the discrepancy is high in the tumor cell compartment and low in the endothelial cell compartment.

However, the preclinical data on tumor angiogenic inhibitors have not been translated very fruitfully into the clinic so far [32]. A possible explanation is that tumor vessels were delimited as augmentation of the angiogenic response by progenitor endothelial cells, and vessel cooption from the pre-existing vessels. Although this form termed angiogenesis plays an important role during the adult repair damaged tissues, it is somewhat in corrector incomplete in tumors. The recent advance has suggested that tumors can generate their own microvascular structures, even without participation by endothelial cells and independent of angiogenesis [33-36]. This form named as vasculogenesis particularly relates to the embryonic development of the vascular system. Taken together, "tumor neovascularization" would be the more appropriate at present.

The gradual emerging evidence demonstrates that tumor vasculatures are chaotic in architecture and abnormal in function [37,38]. Compared with normal vessels, tumor vasculature is often dilated and convoluted, with uneven diameter, excessive branching and shunts. The ultrastructure shows not only that the endothelial cells are abnormal in shape, but also that the intercellular junctions are loose along with a discontinuous or absent basement membrane. These abnormalities tend to make tumor vessels leaky [39]. In addition, blood flow in many tumors is chaotic and variable. Moreover, tumor vasculatures express non-uniform protein surface markers that are absent or barely detectable in mature vessels [40]. The tremendous heterogeneity in structure and function indicated that there existed different latent mechanism between tumor neovascularization and normal angiogenesis, and not yet identical. Meanwhile, the process of tumor neovascularization also lack controllability (self-plasticity) similar to tumor cells. Intriguingly, the experience shows that the capability of the adult normal tissue repair (including normal angiogenesis) is far less than that of tumor growth, thus, it is too difficult to understand for tumor-wide cooperation if the tumor cell replication and the capillary construction act independently.

Last but not least, techniques designed to identify the tumor angiogenesis by the changing tumor microenvironment (*in vitro* and *in vivo* of animals) may not be applicable to the original tumors. Hitherto, we cannot copy any normal tissue or organ under this situation, not to mention tumors, a kind of abnormal tissue. One major importance is to take microenvironment factors of a tumor into consideration [41,42]. The anti-vascular therapy indeed has given rise to one of the most tantalizing perspective because it might lead to radically new treatment regimens to achieve maximal efficacy in the fight against cancer [41,43] and would help to foster a new era of tumor therapeutics in the clinic [44].

Concluding Remarks

In the light of current understandings of human tumor, solid tumor is commonly appreciated as an abnormal mass of tissue as a result of neoplasia which displays uncontrolled growth after initiation and is not coordinated with that of any normal tissues around it. Tumor uniqueness is the abnormality of its cell morphology and aggressive behavior provided by unrestrained division and growth [45]. Indeed, tumor is a disease between the cellular level and the organic level (an abnormal mass of tissue).

Our notion of tumor determines how we will approach its treatment. In search for human tumor carcinogen, scientists have experienced lots of attempts by a variety of methods and techniques. In the last three decades, scientists have learned more about tumor than has been gained in all the centuries preceding. Today, we are fortunate to have available a wealth of information about tumor biology and related knowledge, that all scientific knowledge is based

on the knowledge already acquired by the hard work and discovery of our predecessor. Regretfully, this does not change the fact. We cannot reproduce the trajectory of an individual life. During imitating the tumor formation process, the key challenge is the development of models that incorporate the behavior of the entire tumor [46]. For this, we need new technology but not mastered this technology. This frustration is very obvious. We knew how to study tumor, but do not know how to establish the suitable model organisms for understanding human tumors. We are optimistic that the field of innovative new tumor model will continue to move forwards as we build on recent successes of tissue regeneration. Although the elusive clues for tumor may be a distant dream, the understanding the nature of tumor will favor to developing innovative strategies. We also believe that the mystery of tumor can be unraveled and the tumor can be overcome eventually.

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