COMMENTARY

Hypothesis on the Role of Cytoplasmic "Short Base Sequences" in Carcinogenesis

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Abstract

Cancer is a highly complex medical problem with ramifications for public health throughout the world. Most studies have mainly focused on change in the nuclei as being aetiologically responsible. Few have examined the relationship between the cytoplasm and cancer, despite the fact that research has indicated that the cytoplasmic environment is an important factor for cellular differentiation and that the genetic information provided by the nucleus is entirely dependent on this environment for its expression. Gene mutations may be the result, rather than the cause of carcinogenesis. We submit a new concept - "short base sequences" (50-500 bps, including DNA or RNA sequences) in the cytoplasm which could play an important role in carcinogenesis. This is a new theory to explain the origin of the cancer.

Keywords: Carcinogenesis - cancer stem cell - cytoplasm - short base sequence - susceptible base point - transfection point

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Introduction

One hundred years ago, cancer was a new word for the world, but now it is one of the most talked about words in medical practice. The morbidity and mortality of cancer are much higher than thirty years ago. Cancer initiation and development have been regarded as a multistep process that is incarnated by the progressive genetic alterations that drive the transformation of normal human cells into highly malignant derivatives (Nowell, 1988; Hanahan and Weinberg, 2011).

In the past thirty years, scientists have made considerable progress in cancer research. Starting with the profound discovery of the DNA structure, following the genetic sequencing technology, gene is always the focus of cancer research. And the gene mutation is the most common phenomenon in cancer. Researchers also shifted the concentration from a single gene or several genes to entire genomes with the development of technology (Burton et al., 2007). Genome sequencing results show that there are even thousands of mutational genes in a single kind of cancer (Koboldt et al., 2012). Meanwhile, there is a contradictory phenomenon existing in the gene mutation. Within a period of time, some genes were found to be oncogenes which were considered to be the cause of cancers. But there were also studies showed that the same oncogenes could both promote tumour growth or inhibit tumour growth; some oncogenes can promote the carcinogenesis when active, yet resurrectionary activation of the same oncogene does not induce a new cancer (Weinstein, 2002). Studies pay much more attention to gene mutation than cell mutation.

Therefore, it is not a perfect explanation for carcinogenesis just using the gene mutation theory. This allows us to reflect--why are there so many mutation genes in cancer? Is it the cause or the result of the cancer? Here, we will try to explain the origin of cancer from another aspect in regards to gene mutation as the result of the cancer. And we will submit a new concept--"Short base sequence" (DNA or RNA sequence) in the cytoplasm, which can play an initial role in carcinogenesis.

Roles of the Cytoplasm in Carcinogenesis

Early in 1962, John B Gurdon argued that the cytoplasmic environment could act as the initial factor in cellular differentiation and concluded that the genetic information provided by a nucleus is entirely dependent on it. He indicated the importance of the cytoplasm in cellular differentiation. But in the following years, few scientists pay attention to the relationship between the cytoplasmic and the cancer. In 1994, Hinrich Abken found that short DNA sequences from the cytoplasm of mouse tumor cells could induce immortalization of human lymphocytes *in vitro*. The cytoplasmic DNA sequences have some common properties: (1) they are 50-500 bps in length and of linear configuration, (2) most of them exhibit the potential to modulate the activity of a transcriptional promoter, and (3) the DNA elements are preferentially found in tumor cells, not in cells with normal phenotype (Hegger and Abken, 1995). Therefore, we should pay more attention to the role of cytoplasm in carcinogenesis.

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Cancer Stem Cells

More and more studies show that most cancers may originate from a clonal selection of variant cells by malignant transformation which are called cancer stem cells (Grandér, 1998). These cells are characterized by the ability to be immortalization, infiltrate and destroy normal tissues (Bjerkvig et al., 2005). Although cancer stem cell-like cells have been identified in many forms of cancer (Bjerkvig et al., 2005; Vermeulen et al., 2012), the identity of the normal cells that get the first genetic 'hits' leading to tumour initiation has remained unknown (Perez-Losada and Balmain, 2003). The origin of the cancer stem cells is still a scientific conundrum for the scientists.

"Short base sequence – Transfection" in Carcinogenesis

Because of its cunning characteristic, there are always a mass of cancer cells in the body when cancer is detected. So it is very difficult to find the first cancer cells. In the new theory, we focus on the formation of the first cancer cells which also called the cancer- stem cells.

We classify the carcinogenic factors into non-viral and viral. Non-viral carcinogenic factors can affect the free bases in the cytoplasm by membrane proteins, while the genetic material of virus can be disassembled and cut into base fragments directly after entering the cell. The bases can be assembled to be a linear single-stranded "Short base sequence" (DNA or RNA property). "Short base sequence" transfects the nucleus DNA in "susceptible base point" to form "transfection point". Cancer stem cells are a cluster of cells with the "transfection point". When the transfection point persists, it can result in the mutation of tumor suppressor genes and proto-oncogenes by a waterfall of chain reactions. These genes are the upper stream mutation genes. Then many signal pathways take part in the cancer development. And hundreds of genes mutate along with the activation of signal pathways, which are the downstream mutation genes (Figure 1).

Characteristics of the Theory

In the new theory, the critical point is the formation of the "transfection point" which is decided by the combination of the "Short base sequence" with the "susceptible base point". The concept can be visualized like a "Biological House", the "transfection point" is the key to the "Cancer Room". When opening the "Cancer Room" by the "transfection point" key, we can see a lot of mutational genes in the room. Upper stream mutation genes are the walls--they are important in maintaining the structural stability of the cancer. Downstream mutation genes are the groceries or food inside--they endow the cancer various biological function. So, gene mutation is the result but not the cause of cancer. Mutations are the phenomenon but not the essence. A clue of "carcinogenic factor-- -- short base sequence -- susceptible base point--transfection point—cancer formation" would be helpful to explain the carcinogenesis.

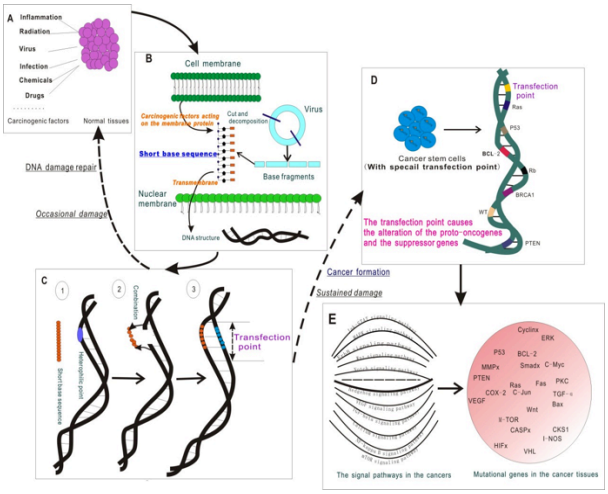

Figure 1. The Schematic Diagram of the "Short Base Sequence" in Carcinogenesis. (A) The susceptible carcinogenesis factors, mainly include the non-viral factors (inflammation, radiation, infection, chemicals and drugs) and virus. (B) The key procedure of the theory. (1) Non-viral carcinogenesis factors assemble the free bases in the cytoplasm to the "Short base sequence". (2) The virus in the cytoplasm is decomposed and cut into some base fragments. (3) "Short base sequence" transfers into the nucleus freely. (C) "Short base sequence" transfected into the DNA in the "Susceptible base point" to form "Transfection point'. (D) The cancer stem cells are a cluster of cells with "Transfection point". When "Transfection point" persists, it results in the mutation of tumor suppressor genes and proto-oncogenes E Various signal pathways participate in the cancer development and a mass of mutational genes can be detected in the cancer tissues

Conclusion

In summary, cancer research discovery mainly abounds in genetic mutation mechanisms these years. But gene mutation may be only a phenomenon of the carcinogenesis. A paradigm shift is necessary concerning the origin of cancer stem cells. So we submit a new concept called "Short base sequence" which may play an important role in the formation of cancer stem cells. In the future, we will launch studies to find the "Short base sequence" and check the authenticity of our theory.

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