A Wake Up Call from the Micro-Cosmo

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Abstract: - How does a normal cell turn into a cancer? What goes wrong? Over the past twenty years, cancer researchers have learned various molecular events that are associated with cancerous phenomena. Researchers have identified a list of critical proteins whose functions are essential for the safeguarding mechanisms at various levels. In cancer cells, many of these proteins are not doing their job: either they are inadequately made or they are somehow mutated. At the very beginning, these findings raised lots of optimism among researchers and the public, with the consideration that the identification of these changes will lead to the cure of cancer, by somehow fixing these molecular defects. However, as researches advance, it is clear that the mistakes are more extensive. Cancer is a system problem. This paper outlined the cancer phenomena from the perspective of a molecular biologist studying a fascinating group of critical regulatory molecules, called the TGF-β. From the most current understanding of how TGF-β exerts her critical effects on growth inhibition and immune regulation at the molecular level, the author suggests that the "mass production mass consumption" state of a cell could be the very foundation for all types of system diseases including cancer. Such a state of existence is manifested at the level of a cancer cell, as well as at the level of human society and the overall state of our physical universe. Is there a cure for cancer? Is there a cure for current social crisis? Is there a way to slow down the cosmic expansion? Do all these problems have a common root? The author suggests that the root for such a multi-system problem lies within the consciousness of modern man. An ancient cultivation practice, Falun Gong (Falun Dafa), has pointed out the fundamental law of the universe, and can guide humanity to embark on the right path for total health.

Key-Words: - TGF-β, proteasome, cancer, consciousness, Falun Gong, Falun Dafa, mind, body, spirit

1 Introduction

As a molecular biologist, I have been studying a family of fascinating molecules, the TGF-β superfamily (1). In the past ten years, the amazing complexity of the signaling mechanisms of this family of proteins and my own personal life events, which interestingly interwoven with the several critical discoveries happened in my research laboratory, urged me to take a more holistic approach to look at the molecules. As a Chinese who was exposed to all types of mind-body practices, I am also open-minded to the eastern paradigm of human body science. This paper is the child of the interaction between the Eastern and Western aspects of my learning and merely serve the purpose for inviting a broader perspective of a critical disease we are all concerned about: Cancer.

2 Problem Formulation

Every cancer researcher is asking these critical questions: what is the cause of cancer and how we can cure cancer. Modern life sciences have taken the approach of dissection of life phenomena and have now delved into the realm of molecules. While the hope was to find the cellular and molecular defects associated with cancer and then formulate methods to combat cancer through cellular and molecular means, we know face the biggest challenge: cancer is not a mere molecular or cellular problem, but a system problem. Then we are facing the question: what is the system with which human body is a part of? The ancient Chinese consider human body is a universe. How can we study cancer as a system disease? With these questions in mind, I here share with the readers my limited understandings.

3 Problem Solution

The solution I am taking, is to increase communication among scientists in many different areas as well as between scientists and the public. I believe that scientists should take an active role in

sharing scientific observations with the public. Below is the tale I will tell.

One early spring day, I was on my way to work. A stranger greeted me and asked me what I do for work. After learning that I am a cancer researcher, his eyes lit up and asked: "Are you going to find a cure for cancer?" It was his question that plunged me into deep thoughts and now I would like to share with you.

For me, ever since my grandmother passed away so suddenly from malignant liver cancer about twenty years ago, the name "Cancer" never left my mind and heart. It was the innocent hope in my young heart for finding a cure that has led me to this stage of my career. Since 1988, I have followed the path of the reductionism-based modern science approach to study Biology at multiple levels: from Anatomy, to Histology, to Cell Biology, and finally to Molecular Biology, using yeast as a model system to study gene regulation. After I obtained my Ph.D. degree, I felt I was ready to be face to face with Cancer, therefore stepped into the field of cancer research, which, like many others, via observing cells in artificial systems (we call *in vitro* systems of cell lines grown in petri dishes).

In 1992, when I started my postdoctoral training at Massachusetts General Hospital in Boston, I "met" this powerful protein called Transforming Growth Factor-β (TGF-β). This molecule is a potent suppressor of cell growth. In our body, there is a large number of TGF-β-like proteins, all of them are very powerful, in that each of them is in charge of the formation and maintenance of different major organs of our body. Most of these proteins are potent inhibitors of cell growth. In our body, there are also a large group of proteins whose functions are to actively promote cell growth. Here the ancient wisdom of China, the theory of the balance of Yin and Yang in Macro-Cosmo, is beautifully reflected at the molecular level, in the Micro-Cosmo of the cell. Research in the past twenty years have led to the elucidation of the detailed molecular network in a normal cell which goes through a highly regulated life cycles of growth, specialization (we call differentiation), aging and death. In every step of the life of a cell, we can "hear the song" and "see the dance" of the interplay of the Yin and Yang factors in great harmony. The disruption of the balance between these two factors is recognized as the foundation for uncontrolled cell behaviors, one of which manifests as Cancer. How does a normal cell turn into a Cancer? What went wrong? For a normal cell, it responds to the environmental cues to determine when it can enter the phase of growth (we call the cell cycle), which consists of several distinct stages (we named them as G1, S, G2 and M). There are gates between each phase. The cell has to meet certain requirements before they can move on.

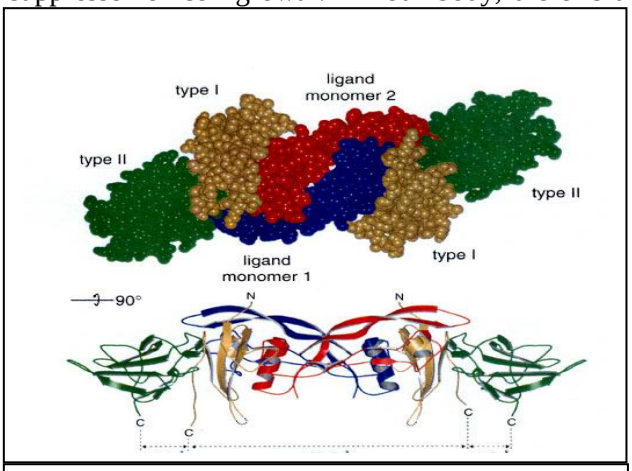

Figure 1. The TGF-β molecule as a dimmer (blue and red) that is bound to two proteins: type I (golden) and type II (green) receptors

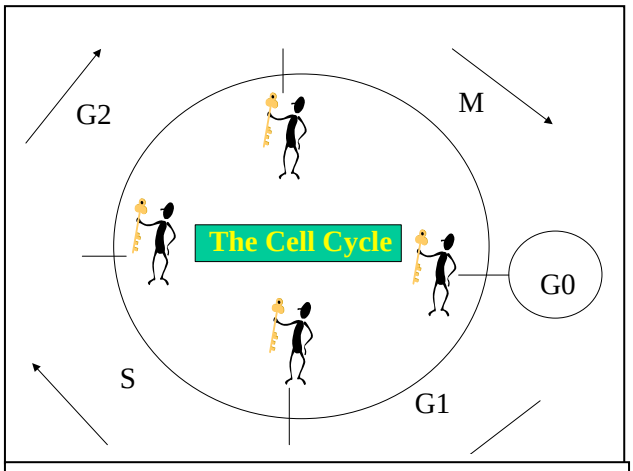

Figure 2. A cartoon to illustrate the four stages a cell goes through when one cell divides into two cells.

These gates are very important, since if there is something wrong in the cell, the gates will serve to safeguard the cell by stopping it at that phase till the problem is somehow fixed. If the problem cannot be fixed, the cell would trigger an alarm system that, program. Thus, a normal cell acts in accord with the system it belongs to; when mistakes occur, the cell has a mechanism to "sacrifice" itself for the benefit of the whole. On the contrary, a Cancer cell somehow outsmart the laws at each gate of check

point between the different phases of growth, therefore continue to grow in number. The death mechanism is also abolished so that they reach "immortality". Of course, such temporary immortality is followed by the death of the whole, thus reflects, interestingly, a very ignorant but totally selfish "spirit".

In the past twenty years, cancer researchers have learned that it takes many steps for a cell to accumulate the various protein mistakes, which eventually wipe out all major safeguarding mechanisms at the level of a cell. Then the cell starts to metastasise, during which it again violates multiple system laws, including the laws of the Immune system, which, like the policeman, normally provides constant surveys of the body system to eliminate abnormal cells.

The real mystery is: why the cell can manage to accumulate so many mistakes without being eliminated? Within the Micro-Cosmo of a cell, we know that there are many safeguarding mechanisms in place. Within the "Mid-Cosmo" of a body, we know that there are also many safeguarding mechanisms in place. Why in a cancer patient, every safeguarding mechanism failed? Some biologists believe that cancer is due to some mistakes at the gene level, which allow the genetic material to be unstable (we call genetic instability) therefore leading to large scale mistakes at the gene level. However, a normal cell knows how to fix a mistake at the gene level and also knows how to initiate death program when it fails to fix the problem.

Many labs, including my own, study how cells communicate with each other via proteins (www.vmresearch.org; "laboratory research"). TGF-β is made by almost every cell in our body. When it is released into the outside of a cell, TGF-β serves as a signal to "instruct" cells which have a unique set of proteins that can recognize and bind to it. Once these binding proteins (we call receptors), which are sitting on the cell surface, binds to TGF-β, these receptors will then "talk" to proteins inside of the cell. The detailed steps of protein-protein communication inside of a cell in response to an outside-of-cell protein are mapped out carefully by many labs in the research community. Such studies belong to the field of what we call "the signal transduction field". After six years of intensive and expensive studies, we now identified an interesting functional mechanism for TGF-β. It is known to everyone in this field that there are a group of proteins inside of the cell, with the name "Smad", are critical for carrying out the instructions of TGF-β to suppress cell growth. In fact, many cancers, such as colon cancer, pancreatic cancer, and head and neck cancer, are all associated with defects of these Smad proteins. Not until recently, we found that Smad carry out its mission through directly talking to an extremely important protein system in the cell. This protein system consists of a large number of proteins all work together to do the following jobs: 1) mark old, aged, or dysfunctional proteins for destruction; 2) help almost every aspect of cellular functions via orderly breaking down proteins to fine-tune the levels of each protein that works as a regulator in the cell. This system also is essential for the immune system to find what is wrong when virus and bacteria enter the body, or when a cell behaves abnormally. This protein system is called "the 26S proteasome system". The malfunction of this system also blocks the function of TGF-β as a suppressor of cell growth.

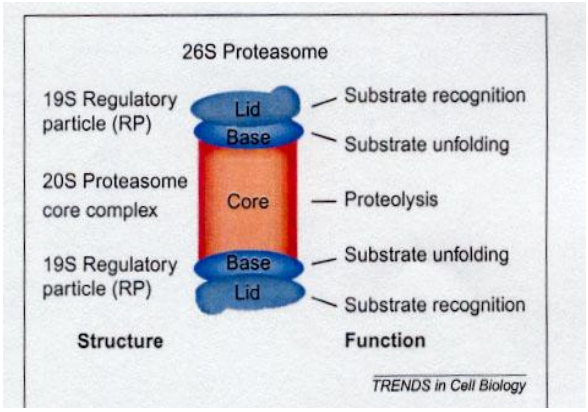

Figure 3. A cartoon to illustrate the shape and the components of the 26S proteasome.

When I was pondering on the meaning of this finding, my friend Dr. Lili Feng called me one day. Lili is an Associate Professor at Baylor College of Medicine. Both Lili and I practice Falun Dafa, an ancient mind-body practice now broadly known to the public due to the recent persecution of Falun Dafa in China (www.falundafa.org). I knew Lili was carrying out a project to examine the effect of practicing Falun Dafa on cells of the immune system. Lili told me that she has completed her studies on comparing the level of 12,000 genes in Falun Dafa practitioners and non-practitioners. To my great surprise, she mentioned some genes in the proteasome system. I therefore asked her to send me the original data and decided to take a careful

look. From that point on, an amazing stream of enlightening information flow into my research system. The data Lili sent to me was a pile of numbers assembled randomly from the experiments. But from the pile of the numbers, one clear image came out: more than 10 different proteins in the proteasome system are drastically reduced in Falun Dafa practitioners' immune cell. This would indicate that the proteasome system is down-sized. It would not make much sense if only this system is down-sized, since the lack of sufficient proteasome system would lead to the accumulation of junk and old proteins. But in the same set of data, more than 10 different proteins that belong to another protein system called "ribosome" are also drastically reduced. Ribosome is responsible for making new proteins. I suddenly realized that the data is suggesting the coordinated down-sizing of the entire pipe-line of proteins production and protein consumption.

Lili then mentioned to me that she has read papers regarding the correlation of proteasome system size and activity with longevity, in mice experiments. Dr. Allen Taylor from Boston University reported that when the food supply was restricted, mice live longer and their proteasome system is down-sized (2-4). I then found a paper that reported the correlation of increased proteasome system activity with many different diseases. In this paper, it was reported that the highest proteasome system activity was found in cancer cells (5). A third paper from Lili added the final touch to an idea that started to surface (see below). In this paper (6), it reports that the careful studies of protein metabolism in a cell suggest that 1/3 of new proteins, after made, are immediately destroyed. Thus, the cell is working in a very busy and wasteful state.

Lili and I started to send emails back and forth. Lili has wonderful humour and wild imaginations. One day she asked me: "you know what is the counterpart of proteasome in the macro-Cosmo of the Universe?" Then she answered for me: " The black hole". Then she sent me a set of reports on how active the black holes are now in the Universe. "You see", she said, "the proteasome are very busy when cells are sick, and what does it mean when the black hole is very busy in the universe?" When I heard that, I thought of the phenomenon of our modern life style: Mass production and Mass consumption. Isn't it amazing that the different cosmic systems of cell, body, society and the entire Universe, from micro to macro, exhibit such striking similarities and correspondence?

At this point, when I went back to think about the question: what makes the cancer cells accumulate so many mistakes and allow it to violate so many different safeguarding mechanisms, the following idea came to my mind: could it be linked to the hyper-metabolic rate of the proteins? If all cells in a body are under the state of mass-production, the proteasome system is likely over-loaded and unable to breakdown old and broken proteins, which then carry out wrong things, which further disrupt the balance. Since the proteins are the real players in all functions of a cell, when bad proteins can not be eliminated, they will continue to do bad things till the entire system is out of control. No matter how hard the cell tries to increase the amount of proteasome production, if the metabolic rate is constantly high, the cell will eventually fail to manage. The increased proteasome level seen in cancer cells likely reflects such a last struggle of the cell to regain the balance.

I can not help wondering how many of the diseases modern people are experiencing are the result of the hectic life style they have, the mental stress they are under, and the endless pursue their mind and heart engage. All these can, through the unique human system of pyscho-neuro-endocrine system, transmit to the cell level to increase the cellular metabolism, which, when overwhelming the proteasome system, leads to the accumulation of cellular mistakes, and finally the downfall of the body system.

Every morning when I go to work by bus, I always sit next to a Chinese Lady, Mrs. Bao, who has recently come to Seattle from Shanghai to visit her daughter. She worked as a nurse-in-chief in a big hospital in Shanghai for more than 20 years. Since she worked with many cancer patients, I asked her whether she has some insights about cancer from her clinical experience. She told me three interesting perspectives: 1) many cancer patients experienced major stress prior to the diagnosis, such as divorce, loss of loved one and the loss of job; 2) ten years ago most of the cancer patients are elderly, but now most are young patients; 3) the young cancer patients die more rapidly than the elderly. I asked her why is this so. "I think it is because of the young people have higher metabolic rate than the elderly." She said with confidence. She then told me how hot the cancer area feels when she tried to chance the dressings for breast cancer patients. I looked at her and realized that it does not always have to take the sophisticated technology to be in touch with the truth.

So, what is the cure for Cancer? Biologists, including myself, no longer have the confidence to claim that we will find the "Magic Bullets" to cure cancer. In the expert review article in the Journal of Molecular Medicine, 1999, Drs. Paul Pharaoh and Carlos Caldas stated: "In the world wide, 10 million new cases of cancer will be diagnosed during the year 2000; unfortunately, the overall survival rate for such patients has changed very little during the past 20 years, despite rapid advances in the understanding of the biology of human cancer". In 2002 Nature Magazine (Nature 416, p470, 2002): "With more than $46 billion spent on cancer research by the US federal government alone… a minority of experts has even begun to suggest that cancer has become science's Vietnam." Fundamentally, cancer is not a simple gene disease, but is a system failure. Since any drug targets a specific protein, a system failure that involves the malfunctions of many different proteins in many different systems can never be adjusted by one simple drug, or by even several drugs in combination.

The results Lili have obtained suggested that Falun Dafa, a mind-body cultivation practice, can down-size, in a coordinated way, the protein production and protein degradation systems. So here is the data to suggest that there is a way to regulate systems, but such a way is not via the application of an external chemical compound, but via doing some self-work. In several experience sharing conferences that I have attended in the past two years, I have met numerous practitioners who experienced healing of "incurable diseases", including cancer. The potent healing effect of Falun Gong practice is well-known in China, even by the Chinese Government, prior to the persecution (7). The phenomenon is striking and demands some serious attention by the medical field. How does it work? What is so unique about Falun Gong? As a practitioner myself, here I can share with you some of my limited understandings. I think that one of the most unique features of Falun Dafa, which makes it stands out from all other mind-body practice, is a complete system of cultivation principals expounded in the main teaching text of "Zhuan Falun", which guides a practitioner to look within oneself in every situation in life, instead of looking outwardly. The practice emphasizes that the fundamental characteristic of the Universe, which is within every particle of the Universe, can be summarized by "Truthfulness-Compassion-Forbearance". Therefore, the goal of a human life is to constantly assimilate with this fundamental characteristic of the Universe. "The entire cultivation process is a process of constantly letting go one's attachments" ("Zhuan Falun"). By looking within oneself to reveal attachments to external rewards, a practitioner choose to let go of the attachments and take the positive perspective on every tribulations. Instead of worrying for self-loss and self-gain, a practitioner gradually step out of this little self and use Compassion to embrace the world. This provides the practitioner the inner strength to face all tribulations with peace and harmony. Such peace and harmony is manifested directly at the level of the cell, by reduced metabolic state of the cell. If the cell is making less proteins, the proteasome will be fully functional in safeguarding the cell in degrading old and damaged proteins and in fine-tuning the levels of each important regulatory proteins in the cell.

Upon sharing some of my thoughts with my high school friend, who is a physicist from Caltech and now working for IBM, who made the following comments: "This down-sizing effect (of Falun Gong practice) seems to agree with the physical law which says the minimum energy state is the stable state. Meditation provides a way of going back to a stable point. The world needs a stabilizing mechanism as well". The past weekend was the tenth anniversary of World Falun Dafa Day. Although Falun Gong has been introduced to the public for only ten years, it is now being practiced by 100 million people through out the world. The Up-holding of Truthfulness sometimes is not easy, as innocent people are dying for their faith for this simple and profound principal; eighty million Chinese practitioners in mainland China are being persecuted. In the recent Science Forum in Boston, someone asked: "What is the purpose of Science?". My answer to this has always been very simple: " Science is a path to find Truth, nothing but the truth." This is the reason I wished to be a scientist when I was young and the reason that I continue to be a scientist, although the "searching for truth" aspect of Science is frequently challenged by the "profit-driven" aspect. I know that some of my peers felt that a scientist should not mix Science with spirituality and social problems and that my mentioning of Falun Gong to the scientific community is a bit out of place. But to me, a scientist should first be a human. A scientist is not a God. We are also held accountable by all universal laws. I believe that Truthfulness-Compassion-Forbearance is the essence of the Universe. So, it is only the most natural thing for me to do, as a scientist, to be outspoken about the Truth, regardless

how we label the Truth within the field of Biology, Spirit or Society.

Figure 4. The lesson from Narcissus: top panel shows how Narcissus was intoxicated by his own image; bottom panel shows the death. Both are paintings by Michelangelo M. da C. (1573-1610)

4 Conclusion

On the cover of an issue of the Science magazine, which was focused upon the topic of the immune system to distinguish between self and non-self, I saw the famous painting by Michelangelo Merisi da Caravaggio (1573-1610), of the Greek Myth of Narcissus (see above colour figure). Narcissus, upon looking into the water, he saw his own image, and then fell in deep love with his own image. To his image, he could not let go, poured in all his attention and consumed all his energy, and finally, he died. At the very beginning, I thought: " Why Narcissus can not tell that this is his own image?" Of course, at that time, I guess they did not have a mirror. But then I asked " why didn't he take a careful look at himself? If he did, he would have found out that there are lots of similarities between his own hands and clothes and those in the image". I then smiled: "How many of us actually will remember to take a look at ourselves in our lives? When we have problems, we looked at everything outside, except ourselves. Birth, disease, aging and death, we all look for answers from outside. We spent so much resource to find the cure for diseases. We are now hoping that someday there will be a super-computer that will enlighten us with the mysteries of life. But, what if this entire physical world is a reflection of a deeper reality? Long time ago, the ancient sages, Buddha, and spiritual enlightened beings have all spoken of a reality that transcends this physical world. Now modern physics have revealed the multi-dimensional nature of the Universe (8). Modern philosophy has also come to the conclusion of the holographic nature of the physical world, including the human brain (9). Biology is in a unique position among all sciences, since it directly study life phenomenon. The knowledge we have gathered at the level of molecules within the Cell has now also revealed the amazing correspondence between the micro-Cosmo of the cell and the macro-Cosmos of the human society and the Universe. Everything in the physical world seems to share a holographic nature that resides beyond this physical world. The understanding and cure of diseases therefore may only come from a new understanding of this ultimate nature of the Universe, which might be also the core of our true self. Modern people are focusing all the attention to the colorful physical world and pursue material gains. The inability of Narcissus to distinguish the reflection of himself from his true self leads to the death of true self.

Have we stared into our own image for too long? Is it time for awakening and a journey back home?

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