

Immune Changes in “Hepatitis Inflammation and Cancer Transformation Process” from the Perspective of Traditional Chinese Medicine

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Abstract: Yin-yang harmony is the core idea of Chinese medicine theory, which has important guiding significance in the prevention and treatment of chronic hepatitis "inflammation and cancer transformation". Modern medicine believes that the change of immune response is one of the reasons affecting tumorigenesis, and intervening the immune response through drugs is the most promising means of cancer treatment for human beings. The yin and yang, collaterals and qi and blood doctrines of Chinese medicine are compatible with the understanding of modern medicine on immunity, especially the concept of replacing "immune-enhancing therapy" with "immune-normalizing therapy", which is consistent with "yin and yang harmonization" to restore the body's vitality. In particular, the concept of "immune normalization therapy" instead of "immune enhancement therapy" has been proposed in recent years, which is consistent with the core idea of "yin and yang harmony" in Chinese medicine to restore the relative balance of the body. This paper discusses the complementary nature of Chinese and Western medicine, with the intention of promoting the development of traditional and modern medicine in the process of preventing and treating "inflammation and cancer transformation" in chronic interventions.

Keywords: Chronic hepatitis, Inflammatory-cancer transformation, Yin-yang balance, Immune balance.

1. Introduction

Primary liver cancer (PLC) is one of the most common malignant tumors, with hepatocellular carcinoma (HCC) being the most common, and the majority of HCC occurs in cirrhosis, where chronic infection with hepatitis B (HCV) and hepatitis C (HDV) viruses is the main cause of cirrhosis, followed by other etiologies, including alcohol consumption and metabolic syndrome-related fatty liver [1]. Long-term chronic uncontrolled inflammation can lead to sustained and low-intensity damage to hepatocytes, which is one of the major causes of induced hepatocellular carcinoma development. The body's immune response is capable of clearing the aggression of curative factors and influencing the damage caused by long-term uncontrolled inflammation. Therefore, changes in the immune system are one of the most important factors influencing the development of the long process of "inflammation-cancer transformation" in chronic hepatitis.

Inner Canon of Huangdi states that "Yin and Yang is the way of heaven and earth, and the framework of all things". It emphasizes that yin and yang are the framework for all changes, and that the secret of yin and yang is the basis for healthy growth of life. Keeping the opposing yin and yang always in the movement of change, fully embodies the understanding of Chinese medicine for the relative static and absolute movement. The immune system can defend against pathogens, recognize and remove senescent cells and cancerous cells in time, but this function can only maintain the physiological normalcy and stability of the organism in an appropriate zone. It can be seen that there are many similarities between the logic of modern immunology and Chinese medicine's understanding of the balance of yin and yang, as well as the pattern of change between evil and positive. In this paper, the imbalance and reconstruction of the immune system in the process of "inflammation and cancer

transformation" of chronic hepatitis will be discussed based on the doctrine of yin and yang of traditional Chinese medicine, and from multiple theoretical perspectives of traditional Chinese medicine.

2. Exploring the Immune Imbalance of Hepatitis "Inflammation and Cancer Transformation" from the Pathogenesis of Chinese Medicine.

2.1 Etiological Perspective

Chronic hepatitis "inflammation and cancer conversion" is a complex process under the joint influence of various factors such as physical condition, environment, emotion and routine. The etiology of Chinese medicine emphasizes that the body's positive qi and the external disease and evil are in opposition to each other and play a role in each other, which coincides with the unification of opposites of materialistic dialectics.

Sanyin Ji Yi Bingzheng Fang Lun said: "six obscurities, the day of the usual gas, the advent of the first from the meridian inflow, within the internal organs, for the external cause; seven emotions, people's common nature, moving the first from the internal organs Yu hair, shape in the form of the body, for the internal cause; such as food and drink hunger and satiety, call call injury gas, all the God measure, fatigue extreme muscle strength, the yin and yang against the trend, and even the tiger and wolf venomous insects, sores, sprains and fractures, the pressure constriction drowning, there is a back of common sense for not internal and external causes. Resistance, resistance and adhesion, fear of pressure and constriction, there is a backwardness to common sense, not internal and external causes." Attributing the etiological factors to three articles can elucidate the various stages of tumor emergence and development process. Viral hepatitis is

the most common cause of hepatocellular carcinoma cells, which keeps the immune system activated and destroys immune self-stabilization and immune balance, which can be regarded as an external cause. Traditional Chinese medicine advocates that the liver is the main "excretion, emotion and will", *Noinclude - yin and yang* should be like the Great Theory" chapter also recorded that "anger injures the liver, joy hurts the heart, thought injures the spleen, worry injures the lungs, fear injures the kidneys," in the process of chronic hepatitis "inflammation and cancer conversion In the process of chronic hepatitis "inflammation-cancer transition", liver lesions lead to abnormal expression of various neurotransmitters and their synthetic enzymes, neuropeptides, hormones, cyclic nucleic acid system and Fos proteins related to the regulation of chronic psychological stress [2], resulting in emotional disorders, which proves the influence of emotions on the disease from the molecular level, and can be regarded as an endogenous cause. Lifestyle, dietary habits and emotional factors have also been gradually proved to be important factors causing the "inflammatory-cancer transition" of chronic hepatitis, i.e. not internal and external factors. It is recorded in *The Origin of All Diseases - Accumulation* that "Accumulation is caused by yin and yang disharmony, weakness of internal organs, wind and evil, and the gas of the internal organs", which summarizes the generation of cancer as yin and yang imbalance, and the human body is always in the balance of yin (pathogenic factors) and yang (resistance ability). If yin and yang are out of balance and the balance of the body is broken, phenomena such as "immune escape" will occur [3], which will gradually increase the risk of cancer. Therefore, once there is an imbalance of yin and yang, yin and yang will compete with each other, which will lead to the continuous deterioration of the disease.

2.2 Pathogenesis Perspective

The immune response is the body's self-protection mechanism, which assists the body in maintaining the stability of the internal environment and in resisting and removing external factors that invade the body. The idea of balance of yin and yang in Chinese medicine highly summarizes the specificity of the immune response. Even if the balance is disturbed, the body will regulate itself autonomously so that it is again in a state of yin and yang equilibrium. As stated in Article 58 of the Treatise on Typhoid Fever, "Whenever you are sick, if you sweat, if you vomit, if you go down, if you die of blood, if you die of fluids. If the yin and yang are in harmony, it will be cured by itself", which emphasizes the idea of balance and moderate coordination of yin and yang.

The defense of the vascular system against injurious factors is the inflammatory response, which regulates the body's microenvironment and helps to maintain a smooth physiological and pathological signaling network. If inflammatory factors, such as tissue damage or infection, are removed, the inflammatory response is terminated and a finely regulated and highly active balance is achieved, a phenomenon known as "controlled inflammation". However, in some cases, such as HBV infection, the target tissue receives a prolonged and low-intensity stimulus, and the body is unable to shift from the mode of anti-infection and tissue damage to a smooth state, resulting in a prolonged or latent

inflammatory response, a phenomenon known as "uncontrolled inflammation" [4]. For example, the most important pathway in the intrinsic immune response that exerts antiviral function is the cyclic GMP-AMP synthase-stimulator of interferogenes (cGAS-STING). cGAS protein senses free HBV nucleic acid in the cell, which then activates the STING signaling pathway. The cGAS protein senses the free HBV nucleic acid in the cell and then activates the STING signaling pathway, which induces the production of type I IFN to clear the virus. After HBV infection, cGAS expression decreases and it is difficult to sense free HBV nucleic acid, so it is impossible to completely eliminate HBV. HBV virus can continue to replicate in the organism and continuously stimulate the cGAS-STING signaling pathway. Continuous activation of cGAS-STING can enhance the pro-cancer NFκB signaling pathway, induce senescence-related cytokines, which are then recruited to immunosuppressive inflammatory cells, ultimately forming an immune microenvironment conducive to the evolution of HCC [5]. When the immune function of chronic hepatitis patients is in a normal state, the risk factors that damage hepatocytes are quickly removed, the positive prevails over the evil, and the state of yin and yang is quickly restored to be stable and peaceful, then it is not easy to develop in the direction of hepatocellular carcinoma; on the other hand, if the immune function is poorly self-stabilized, and the body's yin and yang fight against the positive and the evil, then it will promote the development of "inflammation-cancer transition" in chronic hepatitis.

3. Discussing the Development of Hepatitis "Inflammation-cancer Transformation" from the Theory of Chinese Medicine

3.1 Exploring the Immune Response in the "Inflammation-cancer Transition" of Chronic Hepatitis from the Viewpoint of "qi" in Chinese Medicine

Su Man - The Theory of Stabbing Method has a cloud positive qi exists within, and evil cannot be dried up", *Su Wen - Assessment of Heat Disease Theory* also says that "where evil comes from, its qi must be deficient", indicating that the occurrence of disease is closely related to the prevalence of qi, which is consistent with the theory of immunity, and the malfunction of the immune function can be attributed to the malfunction of qi. In Chinese medicine, according to the source, characteristics and role of Qi, it can be divided into Wei Qi, Ying Qi, Yuan Qi and Zong Qi. "Wei" has the meaning of defense and protection, and Wei qi is named after "Wei", which has the function of protecting the muscle surface and resisting external evils, and is a specific embodiment of modern immune regulation, which is consistent with the three aspects of generation, function and operation of Wei qi. The change of Wei Qi runs through the whole process of "inflammation and cancer conversion".

The prevalence of positive qi is closely related to the lungs, spleen and kidneys of the five Tibetans. The Spiritual Pivot - this collection of clouds: "Wei Qi, so warm flesh, full of skin, fat coupling, the Division of the opening and closing of the person also", "Wei Qi and the flesh of the release of Lee, the skin is soft, the coupling of the dense carry forward", "Wei Qi and the flesh of the release, the skin is soft, the coupling of the

dense carry forward", "Wei Qi and the flesh of the release, the skin is soft, the coupling of the dense carry forward". And "Suwen, cough theory" said: "skin and hair, the lungs of the joint also, the skin and hair first subjected to evil, evil from the joint also", the lungs of the collection and the Wei Qi together constitute the first barrier against foreign evil, to protect the five viscera and six bowels from foreign evil attack. With the study of the body gradually microscopic, the above "skin" also includes the respiratory tract, gastrointestinal tract, urinary tract and other places in the mucous membrane surface layer and part of the lymphatic tissue, the lungs and Wei constitute the first line of defense that is the human body's skin and mucous membrane immunity. The Ling Shu - camp health will be" cloud: "people receive gas in the grain, the grain into the stomach, in order to pass to the lungs, the five viscera and six bowels, all to receive gas, its clear for the camp, turbid for the guard. Although the Wei Qi is released by the lungs to spread, but the growth of the spleen and stomach in the middle jiao [6], modern medicine, the spleen can produce specific immunity required active substances, such as cytokines, interferon, etc., which can be regarded as one of the sources of immune response, at the same time, in modern medicine, the spleen and the digestive tract is an organ with immune function, the spleen can purify the blood, remove pathogens in the blood and the decay or metamorphosis of the cells [7], which is an important part of the immune response. The Yellow Emperor's Classic of Internal Medicine (HUNDI NEIJING) states that "the spleen is the main guardian of the body, and it welcomes food, and it knows the good and bad fortune by looking at the lips and tongue", which shows that the spleen is not only the source of qi and blood biochemistry, but also can be directly involved in the process of protecting the body, which shows that there is a resemblance between the spleen in traditional medicine and in modern medicine. The Spiritual Pivot-Ying San Huisays: "Ying goes out of the middle jiao, Wei goes out of the lower jiao." The word "out" here means "root", and although Wei qi is fed by the water and grain essences that are transported by the spleen and stomach, it is initially derived from the Yuan qi stored in the kidneys. Research in modern medicine shows that T cells, B cells and other immune cells involved in the immune response are generated by the bone marrow, and Chinese medicine theory coincides with the view that "the kidney is the main bone", "marrow" [8]. Genetic energy is the innate energy, inherited from parents, the individual's immune ability and tendency to cancer are affected by genetic inheritance, so the influence of the kidney on the Wei Qi is particularly important. Lungs, spleen and kidney directly affect the prevalence of Wei Qi, directly involved in maintaining immune balance and regulating immune changes, while the liver has an important role in the transformation of chronic hepatitis "inflammation and cancer". Liver is the main excretory, regulates the whole body's qi, makes the qi smooth, elevates and lowers with degree, and has a section, ensures the normal operation of qi, blood and fluid, and makes the body resist external evils, and the ability to clear the internal disease play normally. In the "inflammation and cancer transformation" of chronic hepatitis, abnormal mood change is a very important factor, and the liver is the master of emotion, which can keep the emotion normal and play an important role in the prevention and treatment of tumor [9]. The core disease of chronic hepatitis "inflammation and cancer transformation" is located in the liver, and it is related to the lungs, spleen and kidneys, and

each stage will produce a certain degree of damage to different organs, so the prevention and treatment process should not be limited to the liver only, but should be based on the whole, and pay attention to the adjustment and protection of the whole.

3.2 Discuss the Developmental Process of Chronic Hepatitis "Inflammation and Cancer Transformation" from Chinese Medicine Collaterals Science.

After the summarization and generalization of medical practitioners in successive dynasties, the doctrine of collateral veins has become an important part of Chinese medicine, which provides good guidance in the diagnosis and treatment of modern difficult and complicated diseases [10]. The collateral veins are crisscrossed throughout the body, which are the links between qi, blood and internal organs, and have the functions of infusing qi and blood and transmitting information [11], which are similar to the functions of blood vessels and nerves in modern medicine. Therefore, the smooth and stagnant collaterals, the normal popularity of qi and blood is the basis of the collaterals system to maintain the normal life activities of the human body. In modern medicine, the function of blood vessels in transporting blood and immune cells can be attributed to the theory of collaterals. Early chronic liver disease patients are mostly due to excessive alcohol and food, liver and gallbladder dampness and heat, or depression, liver qi stagnation, so that stagnation of qi, long-term disease is blocked and damaged, leading to further development of the disease. For example, in the chronic hepatitis "inflammation and cancer transformation" process of liver fibrosis stage, liver sinusoidal endothelial cells function abnormally, resulting in liver sinusoidal capillarization, at the same time, the extracellular matrix (ECM) generation and degradation of the balance is broken, and further promote the liver sinusoidal capillarization, so that the hepatocytes are in the state of continuous hypoxia and ischemia. Due to the reduced blood transportation, the concentration of immune cells concentrated in the liver decreases, the immune balance is broken, and the tumor cells cannot be recognized and eliminated in time. When hepatocellular carcinoma enters the late stage, the local hypoxia of the organism intensifies, increasing the expression of hypoxia inducible factor-1 (HIF-1), which elevates the expression of its downstream vascular permeability factor (VPF), and ultimately leads to an increase in tumor angiogenesis [12]. Tumor vasculature will assist the spread of cancer cells to other sites [13], further disrupting the immune balance. Evil to the liver complex leads to obstruction of qi and blood operation, breaking the balance of yin and yang maintained by the organism; therefore, in the prevention and treatment of tumors, attention should be paid to removing the factors that obstruct the liver complex, so that the balance of yin and yang in the organism can be reconstructed.

4. Discussion of Immunotherapy for Hepatitis "Inflammation-cancer Transformation" from the Perspective of Balance in Chinese Medicine

4.1 Supporting the Right and Dispelling the Wrong and Harmonizing Yin and Yang are the Core Ideas for

Restoring the Body's Immune Balance

At the beginning of the anti-tumor phase, human beings focused on the "immune-enhancing method" to strengthen the attacking power of immune cells. However, an over-activated immune system also breaks the balance of yin and yang in the human body, and poses a danger to the organism that is almost equivalent to an inactive immune system. Chinese medicine emphasizes the importance of the relative balance of yin and yang in the body, and through the intervention of traditional Chinese medicine, the imbalance of yin and yang can be re-established as a homeostasis. Through the experience of treating a large number of metastatic tumors and combining the characteristics of Chinese and Western medicine, some researchers have proposed the "balance blocking" method, which believes that it is necessary to monitor the process of tumor transmission, and achieve the immune balance of Western medicine and the balance of yin and yang of traditional Chinese medicine by supporting the positive and eliminating the evil, and regulating yin and yang, in order to block the changes of the tumor [14].

Cancer development is not simply passive with the change of immune response, but actively applying various ways to delay, weaken or even stop tumor immunity, leading to the failure of tumor growth inhibition, i.e., "immune escape", which is one of the key points in understanding tumor development at the immune level [15]. After experimental research found that the over-activated immune system also exists a huge danger, based on which the concept of human tumor treatment gradually from the enhancement of immunity to restore the direction of immune normalization. T cells in the human tumor immunity plays a crucial role in the organism, there is a group of cell surface molecules in the organism can recognize normal cells and tumor cells, and have an inhibitory effect on over-activation of immune response, thus eliminating tumor cells and protecting the body from tumor growth. Thus, they destroy tumor cells while protecting their own normal cells, these molecules are called immune checkpoints [16], immune checkpoint inhibitors can restore the function of immune checkpoints in recognizing tumor cells to normal, awakening the attacking power of immune cells and normalizing the immune response, and this program has become one of the main means of treating cancer. For example, in physiology, the programmed death-1 (PD-1) and its ligand (PD-L1) pathway arose because of the need to control the degree of inflammation at the site of expression of an antigen in order to protect normal tissues from damage. The binding of PD-1 to PD-L1 leads to the inhibition of T-cell receptor-mediated lymphocyte proliferation and cytokine secretion through the inactivation of the phosphatases SHP-2 and Zap70 [17]. Upregulation of PD-L 1 expression through PTEN silencing and serine/threonine kinase Akt activation will also inhibit the transport of additional T cells into the tumor microenvironment, preventing T cell overreactivity [18], and providing a protective effect on normal cells. This protective mechanism is distorted through the overexpression of PD-L1, thus avoiding an immune response to the tumor. The use of PD-1/PD-L1 inhibitors blocks the binding of PD-1 to PD-L1/2, thereby preventing the activation of PD-1 and its downstream signaling pathways. It also restores immune function by activating cytotoxic T cells and their mediated immune responses [19]. In conclusion, the concept of immune

normalization is not to strengthen the immune response, but to regulate the immune balance on the right track, emphasizing that the immune microenvironment should be developed into a dynamic balance in the treatment of tumors, which is compatible with the prevention and treatment viewpoints of Chinese medicine that advocates the harmonization of yin and yang, and it establishes a brand new direction of development for the treatment of tumors.

4.2 Individualized Treatment and Multi-targeting Effect of Chinese Medicine

The process of "inflammation-cancer transition" in chronic hepatitis is affected by many factors, and the intrinsic mechanism is complex, the mechanisms of immune surveillance and immune escape have not been fully elucidated, and only a portion of the patients have been treated with good results, and there are related adverse effects. It is limited and stereotypical to understand tumor occurrence, development and treatment only from the point of immune regulation [20]. When Chinese medicine regulates the immune response, it has the characteristics of multi-components, multi-targets and multi-pathways [21]. In the prevention and treatment of malignant tumors, the use of traditional Chinese medicine follows the principle of "supporting the positive and dispelling the evil, harmonizing yin and yang", and the main mechanisms include: enhancing the body's autoimmune ability, i.e., "supporting the positive"; directly attacking the tumor cells, affecting the DNA and protein synthesis of tumor cells, and influencing the metabolism of tumor cells, which are the most important factors for cancer-causing factors. The main mechanisms include: enhancing the body's own immune ability, i.e., "supporting the positive"; directly attacking tumor cells, affecting tumor cell DNA and protein synthesis, influencing tumor cell metabolism to target cancer-causing factors, etc., i.e., "dispelling the evil", and then supplementing with methods of dispelling dampness, resolving blood stasis, warming the yang, dispersing the nodules, etc., to regulate yin and yang, so as to give full play to the systematic and holistic characteristics of traditional Chinese medicine, and to make the use of traditional Chinese medicine to enhance the effect of the prevention and treatment of tumors [22].

Targeted drug is to block a specific signaling pathway or receptor, so that the drug acts on specific tissues and organs to improve drug efficacy and reduce the damage to normal cells. Currently, tumor-targeted drugs mainly block a certain receptor or pathway, and lack of holistic, this treatment can not be absolutely effective in dealing with the complex and changing situation of malignant tumors. Moreover, the current chemotherapeutic drugs are aggressive to normal cells in other parts of the body while attacking and killing tumor cells, resulting in serious side effects after tumor treatment. However, the concept of meridian attribution and meridian-inducing drugs in Chinese medicine can precisely make up for this shortcoming. In the process of using traditional Chinese medicine, each kind of medicine is selective to the internal organs and meridians, and some traditional Chinese medicines can guide or change the action parts and focus on the therapeutic effect of other medicines, which is called "meridian-inducing medicine". You Zaijing mentioned in his book "Reading the Book of Medicine" that:

"A soldier without a guide cannot reach the realm of the thief, and a medicine without a guide cannot pass through the place of disease." The main purpose of the use of the introduction of drugs is to enable the drugs to accurately act on the lesion site, which is in essence the concept of macro-targeting [23]. The existing chemotherapeutic drugs, while attacking and killing tumor cells, are aggressive to normal cells in other parts of the body, resulting in serious side effects that often occur after tumor treatment. Therefore, in the process of tumor treatment, under the premise of complying with the diagnosis and treatment, some meridian-inducing medicines are used to concentrate the medicines in the treatment area, so as to achieve the purpose of enhancing the therapeutic efficacy and reducing the toxic side effects. For example, Chaihu, as a hepatic meridian-inducing drug, can inhibit the exocytosis of P-glycoprotein and promote the absorption of drugs, which can enhance the antiviral and hepatoprotective effects[24]; licorice sweetener and licorice hypochlorous acid, which are purified from licorice in Xiao Chaihu Tang, which is based on the monarchical drug of Chaihu, are known for their ability to protect hepatocytes, improve hepatic function, and lower alanine aminotransferase (ALT) [25]. induced meridian medicine, but can play its important role in the treatment of hepatocellular carcinoma. The use of traditional Chinese medicine has an excellent prospect for regulating the "inflammation-cancer transition" in chronic hepatitis.

5. Concluding Remarks

In summary, immune response has different degrees of influence on each stage of "inflammation-cancer transformation" of chronic hepatitis. Although Chinese and Western medicine have different theoretical bases for the understanding of immunity, they are not absolutely opposed to each other [26], and both of them emphasize the same balanced and harmonious state for resisting diseases and restoring the normal state.

Currently, there is a lack of absolutely stable and side-effect-free solutions for the treatment of tumors in western medicine, so it is the best time to intervene before the formation and development of tumor cells, which is very suitable with the theory of "treating the disease before it develops" in Chinese medicine. Chinese medicine can regulate the balance of yin and yang in the human body from a holistic viewpoint, and it is able to recognize the evidence at each stage of "inflammation and cancer transformation" and adjust the treatment mode in time, and it is not easy to produce side effects and drug resistance. In the future, we should give full play to the role of multiple pathways and components of traditional Chinese medicine, and combine them with modern medical treatment methods to maintain the normal functioning of the immune system from multiple perspectives to prevent and control the whole process of "inflammation and cancer transformation" of chronic hepatitis.

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