MINI-REVIEW

Contradictory Relationships between Cancer and Normal Cells and Implications for Anti-cancer Therapy

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Abstract

Cancer treatment remains a serious problem worldwide. Analysis of the relationship between cancer cells and normal cells reveals that these two share characteristics in contradiction, thus could be analyzed by using contradictory principles. Under the theory of contradictory principles, induction of a dormant state or reversal of cancer cells is an important treatment strategy beyond traditional cytotoxic therapy. Normal cells are also the targets and under the influence of anti-cancer treatments and should be considered during therapy. Findings based on crosstalk between these two cell types may offer opportunities for the development of new biomarkers and therapies.

Keywords: Cancer treatment - contradictory principle - cancer cell - normal cell

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Introduction

Developing effective anti-cancer therapy is a worldwide challenge. Cancer cells have often been the sole focus of studies investigating anti-cancer treatments. However, the relationships between cancer cells and surrounding normal cells (e.g., fibroblasts, vascular endothelial cells, and inflammatory cells) have not been thoroughly studied. Cancer cells and these peripheral normal cells coexist in patients and thus there must be intracellular communication between the differing cell types. Here, contradiction theory was used to explore the relationship between these two types of cells. This may deepen understanding of malignant disease and provide reference data for the development of anti-cancer therapy in clinical practice.

Current State of Cancer Therapy

Common anti-cancer therapies include chemotherapy, radiotherapy, and surgery, which most often target cancer cells. However, these therapies have three shortcomings in clinical practice: First, they lack specificity when destroying cancer cells, meaning that they simultaneously kill normal cells. Second, cancerous cells are not usually completely eliminated. The residual tumor cells develop resistance to treatments, resulting in treatment failure, tumor recurrence, metastasis, and death. Third, anti-cancer treatment itself may promote invasion and metastasis of residual cancer cells and even accelerate the progress of the disease. For example in hepatocellular carcinoma, chemotherapy, radiotherapy, palliative surgery, and hepatic artery ligation induce ischemia and reduce the number of cancer cells in the patient for a short period of time but these techniques also significantly increase the likelihood of invasion and metastasis of the remainig cancer cells. The angiogenesis inhibitor Sorafenib is the first and the only first-line targeted drug for systemic chemotherapy against advanced liver cancer. However, clinical observations indicate that this drug can induce tumor cell resistance and promote tumor cell invasion and metastasis (Kowanetz et al., 2012; Zhai and Sun 2013). Clinicopathological analysis confirmed that ischemic liver cancer cells upregulated CD147 oncoprotein expression, which is closely associated with drug resistance and invasiveness. Upregulated CD147 expression promoted metabolism and invasion of ischemic liver cancer cells. In addition, the upregulation of CD147 was found to be associated with activation of the CD147 promoter by hypoxia-inducible factor-1 (HIF-1), which is induced by hypoxia (Fei et al., 2012). This suggests that hypoxia-induced CD147 protein expression may be an important mechanism by which drugs aimed at inhibiting tumor angiogenesis can simultaneously promote tumor cell resistance and metastasis. Explanations for the aforementioned dichotomy in anti-cancer therapy are complicated. One of the problems in disease epistemology is that cancer cells are usually viewed as deviants that are different from healthy cells and the rest of the human body, leading to the concept of complete destruction of cancer cells as the underlying rationale of various anti-cancer therapeutic strategies. However, the relationship between cancer and normal cells has often been overlooked. New perspectives on and the concepts of malignant human disease and of the development of anti-cancer treatments are urgently needed. Cancer research conducted according to the

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contradiction principle may lead to a more comprehensive and profound understanding of various human cancers

Cancer and Normal Cells Viewed from the Contradiction Perspective

Cancer cells do not exist in isolation but rather coexist with normal cells. The contradiction principle indicates that cancerous and non-cancerous cells should be viewed in terms of two-way conflicts. Interactions between and influences exerted by both parties promote motion, change, and development. The direction and outcomes of this development are usually determined by the main characteristics of the conflicts. When the conflicts are extreme, the contradictory unity disintegrates, resulting in the destruction of the unity, or the replacement by a new contradiction unity. The following are the four most representative basic relationships between any two parties in conflict. Whether cancerous and normal cells have the characteristics of contradictory unity, and the implications that this may have for anti-cancer ideas and strategies, are discussed here.

Conflict between cancer and normal cells

Although cancerous and normal cells coexist in the human body, they are significantly different from one another. Cancerous cells have abnormal morphology and function wheras normal cells have normal morphology and function. Both types of cells compete for limited resources and space. A gain by one party is a loss for the other. The struggle between both cell types creates an unstable condition in cancer patients. If the normal cells (e.g., immune cells) defeat cancer cells, leading to a reduction in the number of cancer cells, the disease is relieved or cured. If cancer cells dominate and grow, normal cells are encroached upon and destroyed by the cancerous cells. Confrontations and struggles between cancer and normal cells are significant, and they have the fundamental properties of conflict between two cell types.

Interdependence between cancer cells and normal cells

When normal cells transform into cancer cells, they induce the proliferation of surrounding endothelial cells. Newly generated blood vessels provide nutrients to further promote cancer cell proliferation. This feed-forward cycle continuously and simultaneously promotes growth of cancerous cells, which then induce additional neovascularization. Fibroblasts in the microenvironment near the tumor cells may also be stimulated to proliferate, providing further supportive structures and interconnecting tumor cells. In this way, cancer cells and their peripheral normal cells are interdependent on each other.

Studies have confirmed that cancer cells and nearby normal cells interact with and depend upon each other through various signaling molecules and signaling pathways. For example, CD147, also known as extracellular matrix metalloproteinases (MMPs) inducer, causes fibroblasts adjacent to cancer cells to produce and secrete MMPs. MMPs dissolve matrix proteins to free space for the proliferation of the tumor and vascular endothelial cells. Conversely, MMPs also cause tumor cells to synthesize and secrete CD147. This secreted CD147 further promotes the synthesis and secretion of MMPs by fibroblasts. In this way, a positive feedback loop forms between tumor cells and fibroblasts, with CD147 and various MMPs as the molecular basis. This positive feedback mechanism promotes endothelial cell proliferation, angiogenesis, and tumor growth (Kesavan et al., 2004) [4]. Another positive feedback mechanism between CD147 and insulin-like growth factor-1 (IGF-1) has been observed between cancerous and endothelial cells, and it also promotes the proliferation of tumor and vascular endothelial cells (Chen, Gou et al., 2012). Recent studies identified a key molecule in tumor cells, serine-arginine protein kinase 1 (SRPK1), which is one main regulator of angiogenesis (Lucas et al., 2014; Brakspear et al., 2014; Brimacombe et al., 2014). SRPK1 can splice the pre-mRNA of vascular endothelial growth factor (VEGF) into pro-angiogenic mRNA. After translation into VEGF, VEGF protein is secreted into the extracellular space to promote formation of new blood vessels. Exosomes are cell-derived membrane microvesicles that contain proteins, DNA, and RNA. According to previous studies, exosomes released from cells are considered a form of cellular waste disposal. However, more recent studies demonstrated that tumor cells released exosomes that were able to fuse with a variety of surrounding cells, allowing tumor cells to communicate with other surrounding cells by disgorging the contents of their exosomes into these cells. This mechanism promotes drug resistance, tumor metastasis, mesenchymal cell proliferation, and angiogenesis(Kahlert and Kalluri 2013; Sloane et al., 2015). Cancer cells and the adjacent normal cells are interdependent on each other, suggesting that these normal cells should be included as an important content in cancer research.

Balancing in growth and decline of cancer and normal cells

Cancer cells escape the constraints of normal cells and develop sequentially into carcinoma in situ (CIS), early invasive, advanced, and metastatic tumors. This can be considered part of the gradual progression process by which tumor cells gain selective advantages in the conflict. Conversely, with an increase in number and activity of immune cells, tumor cells may be killed and eliminated by the immune system. This can be considered part of the gradual progression process by which normal cells become the dominant side of the conflict. Clinical evidence and basic research have shown that the interaction between immune cells and cancerous cells in the tumor microenvironment can largely determine the direction of development of the tumor (Ardiani et al., 2014).

Some cancer patients remain asymptomatic for quite a long time before diagnosis. After anti-cancer therapy, patients may achieve remission due to a decrease in tumor burden and entrance of tumor cells into a dormant state. This dormant state can be considered a contradictory equilibrium between normal and cancer cells under certain conditions. Maintenance of the dormant state to control and stabilize tumor growth may be a suitable therapeutic option for some cancers.

Mutual transformation between cancer and normal cells

Cancerous cells transform from normal to malignant cells in response to carcinogens. One recent study showed that cancer cells can be "contagious" to surrounding normal cells and cause them to become cancerous (Sugimoto et al., 2014). In this case, the researchers collected the exosomes secreted by tumor cells, mixed them with normal cells, and injected them into mice. Results showed that this method induced carcinogenesis in normal cells. One possible mechanism underlying this effect may be that the short RNA fragments in the exosomes affect gene expression in normal cells. These findings suggest that the first clonal proliferation of cancer cells may induce the transformation of surrounding normal cells into cancerous cells at different stages of development. In this way, the enormous number of cancer cells in a tumor might include cells that originated from various normal cells. However, the transformation of normal cells into cancer cells may be reversible. Clinical observation showed that a variety of cancer cells could undergo differentiation and transition back into normally functioning cells under natural growth conditions even in the absence of any anti-cancer treatment. Laboratory research also confirmed that various medications could restore the differentiation of a variety of cancer cells and subsequently cause the cancer cells to revert to normal cells through various pathways (Wojtowicz-Praga 1997; Yin, Shen et al., 2013) Mutual transformation between cancer and normal cells is consistent with the characteristics of conflict and reversal between cancer and normal cells. The induction of tumor cell differentiation and reversion of cancerous cells to normal cells may provide a new direction for anti-cancer therapy in clinical practice.

In summary, the relationship between malignant cells and normal cells has the basic characteristic of contradiction between two parties. Therefore, the contradiction principle may be used for guidance in anti-cancer treatments.

Anti-cancer Treatments Under the Guidance of the Contradiction Principle

Elimination is not the only means of dealing with cancer cells

Cancer patients are contradictory unities made up of cancer cells and normal cells. Anti-cancer treatment must serve the patient; the ultimate goal is the patient's survival and quality of life. Although complete elimination of cancer cells and retention of all normal cells is the optimal therapeutic outcome, existing anti-cancer strategies do not completely eliminate cancer cells and even induce tumor cell resistance to treatment and promote cancer cell invasion and metastasis. Furthermore, traditional non-targeted therapies are also toxic to normal cells, manifesting as the side effects typically associated with anti-mitotic and anti-metabolic agents. However, killing tumor cells is not the only option. Currently, the concept of stabilizing disease and living with non-progressing cancer is widely recognized by international researchers. In 2009, Robert A. Gatenby published a review article entitled "A change of strategy in the war on cancer" in Nature in which he proposed to control tumor growth rather than eliminate the tumor. In addition, he proposed an important perspective with landmark significance in the field that tumor eradication may promote cancer resistance and relapse (Gatenby 2009). Undisturbed and stabile disease maintains contradictory unity appropriately.

To date, the strategies used to control cancer cells have involved the induction of reversal or the dormant status of cancer cells. Induction of tumor cell reversal is a very promising strategy. In 1988, the Shanghai Cooperative Group used retinoic acid to successfully induce acute promyelocytic leukemia cells to differentiate into normal cells. Since then, all-trans-retinoic-acid-induced ATRC-induced differentiation is the preferred therapeutic strategy against acute promyelocytic leukemia. Arsenic can also induce leukemia cell differentiation and apoptosis. At present, the combination therapy of ATRC and arsenic trioxide (known as "Shanghai Plan" in Chinese) has improved the five year disease-free survival rate of patients with acute promyelocytic leukemia from approximately 25% to approximately 95%. This strategy has also become standard worldwide. Although it has been difficult to elucidate the mechanism by which this differentiation takes place and to produce ideal transformation conditions, many scientists believe that the reversion of cancer cells may be the best anti-cancer strategy posed to date. The induction of cancer cell dormancy is a practical means of stabilizing the disease so that the patient may live with controlled cancer indefinitely. Tumor dormancy in cancer therapy has been proposed in academia. This strategy includes three kinds of induction mechanisms: cellular, vascular, and immunological. These three mechanisms have been investigated in clinical studies and all three have demonstrated a preliminary efficacy in anti-cancer treatment (Flaig et al., 2013).

Normal cells as the targets of anti-cancer treatment

Because cancer cells and normal cells are interdependent upon one another and work in opposition to each other, anti-cancer treatment should also involve regulation of normal cellular function in addition to blocking the promotion of cancer cell proliferation. In this sense, normal cells should also be a treatment target. Throughout the body, anti-cancer treatments should focus on maintaining a positive and optimistic state of mind in the patient and improve the functions of the nervous, endocrine, and immune systems, thereby promoting post-traumatic growth (Cowlishaw et al., 2014; Lee et al., 2014). Locally in tumor lesions, anti-cancer treatments should directly eliminate cancerous cells, disrupt microenvironments that favor tumor cell survival, and interfere with factors that can cause metastasis. Regulating the microenvironment can indirectly induce cancer cell death or dormancy. This field of research has received more attention in academics and has drawn results in academic settings. The VEGF receptor (VEGFR) inhibits vascular endothelial cell proliferation adjacent to tumor cells and blocks the blood supply to the cells (tumor starvation). This strategy typically targets normal cells. Currently, there are seven kinds of small-molecule VEGFR inhibitors approved by the U.S. Food and Drug

Administration (FDA) for clinical anti-cancer treatment (Zhang et al., 2014). New drugs that inhibit the synthesis and secretion of MMPs and other factors, especially growth factors in the surrounding tumor surrounding cells, are under development. Strengthening the immune system can also activate a variety of anti-cancer signaling pathways and thus trigger anti-cancer effects (Qiu et al., 2015). Together, these factors confirm the importance of targeting normal cells in anti-cancer treatment.

Impact of killing cancer cells on normal cells

Of the anti-cancer treatment strategies, killing cancer cells has no absolute targeting but conflict effects on both cancer and normal cells. For this reason, the impact on normal cells must be taken into account when deciding between treatment strategies. Many drugs chemotherapy agents have been shown to exert carcinogenic effects on normal cells while they kill the cancer cells. Similarly, it is well known that radiotherapy causes secondary malignancies. Recent studies have shown that chemotherapy may damage the DNA of peripheral normal cells surrounding cancerous cells. These injured normal cells may secrete WNT16B protein into the tumor microenvironment. Once WNT16B is absorbed into the cancer cells, it induces survival by promoting tumor cell growth and invasion and fostering resistance to chemotherapy (Campisi et al., 2012). These results indicate that normal cells in the tumor microenvironment are also involved in inducing tumor cell metastasis and resistance to chemotherapy. The inhibition of normal cell damage by chemotherapy drugs and the secreted factors such as WNT16B protein are important strategies against drug resistance and tumor metastasis (Price et al., 2013). Further research on the impact of anti-cancer treatment on the peripheral normal cells that may indirectly promote drug resistance and metastasis in residual cancer cells, will be necessary.

New areas of research on signaling and regulatory networks between cancer and normal cells

As mentioned above, the tumor microenvironment contains a variety of soluble molecules, exosomes, and other signaling molecules secreted from both tumor and normal cells. It also constitutes the basis of a complicated regulatory network between cancer cells and normal cells. This regulatory network is the material basis for mutual influence and interaction in conflicts between both cell types. The regulation of positive feedback promotes both cancer and normal cell proliferation and tumor development. This has inspired research into the signaling and regulatory networks of both types of cells. The identification of these signal substances and details of the regulatory mechanism may help clinicians screen patients for the molecular markers of cancer and monitor tumorigenesis. They may also help researchers develop new molecular biological treatment strategies. For example, blood and other bodily fluids can be used to detect the exosomes secreted by cancer cells, and they may also be a new way of detecting tumor markers (Sloane et al., 2015). Tumor microenvironment blockage, such as interrupting the secretion of VEGF by cancer cells and MMPs by normal cells, is an important step in disrupting the positive feedback cycles between cancer and normal cells.

In short, comprehensive studies based on the contradictory unity of signaling molecules and regulatory network between cancer and normal cells in the tumor microenvironment are more conducive than simply focusing on cancer cells or normal cells in research. Due to the complexity of the relationship between cancer and normal cells, treatments that address a single target or single signaling pathway will certainly be replaced by combination therapies(Pavelic, 2014). For example, the computational analysis of hepatocellular carcinoma (HCC) in a clinical study showed that the signaling pathways of immune system and the signaling pathways of cancer cells were most closely related. This analysis also suggested that combination therapy using Sorafenib and immune activation is better than chemotherapies associated with existing anti-HCC therapeutic strategies (Ye et al., 2009; Du et al., 2014; Xia and Mao 2014). Clinical evidence has shown that traditional Chinese medicine (TCM) can target multiple types of cells and function through multiple mechanisms. This same evidence demonstrates the unique advantages of anti-cancer treatments that intervene with the tumor microenvironment. Further research into anti-cancer treatment using TCM may be worthwhile [22]. The development and use of new technological methods, such as computational technology and microfluidic chip technology, may be necessary for studies of the contradiction unity of the tumor microenvironment (Cheng et al., 2014; Skinner et al., 2014).

Conclusion

The contradiction principle is a universal philosophical principle that can be applied to cancer analysis and cancer research. In a cancer patient's body, cancer cells and normal cells coexist and have conflicts based on the different basic properties in both cell types. In this way, the cancer patient can be considered a contradictory unity composed of tumor cells and normal cells. The use of the contradiction principle in the development of cancer research may facilitate a more comprehensive and in-depth understanding of the relationship between both types of cells. It may also provide macro philosophical guidance for basic cancer studies and cancer treatments.

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