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Cancer Reversion Therapy: Redefining the Fate of Cancer and Oncology

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Abstract

Cancer, a malignant neoplasm defined by the uncontrolled proliferation of cells and their monoclonal progenies, remains one of the leading causes of human mortality worldwide, owing to its aggressive invasion of healthy tissues and the significant morbidity it engenders. Notably, recent epidemiological trends indicate a downward trajectory in cancer incidence and mortality, attributable to advances in early diagnosis, heightened public awareness, and progressive therapeutic innovations. Current standard-of-care treatment modalities encompass chemotherapy, radiotherapy, surgical intervention, stem cell therapy, immunotherapy, hormonal therapy, and combination therapeutic regimens. Nevertheless, these approaches are associated with considerable limitations, including systemic toxicity, drug resistance, and adverse effects on patients' quality of life. In response to these challenges, ongoing technological advancements have catalyzed the exploration of novel therapeutic strategies aimed not only at eradicating malignant cells but also at preserving and enhancing overall patient well-being. Among these emerging approaches, cancer reversion therapy has garnered considerable attention as a promising and innovative strategy, offering renewed hope for improved clinical outcomes in cancer patients. This review highlights the mechanistic foundations, current progress, and future prospects of cancer reversion therapy as a transformative modality in oncological care.

Keywords: Cancer, cancer reversion therapy, chemotherapy, immunotherapy, malignant, oncology, therapeutic strategies

1. Introduction

Cancer is a malignant neoplasm characterized by uncontrolled proliferation of cells and their monoclonal progenies. It rapidly invades healthy tissues, causing significant morbidity and mortality. Of late, it has been revealed as one of the leading causes of human mortality. There have been 20 million new cancer cases and 9.7 million cancer-related deaths worldwide till 2022[1]. However, cases have shown a downward trend, largely due to early diagnosis, therapeutic advancements, and increased awareness, among other factors. Current data indicates that in 2025, 48% were prostate, lung, and colorectal cancers in men, while 51% were breast, lung, and colorectal cancers in women. The current treatment strategies include chemotherapy, radiotherapy, surgery, stem cell therapy, immunotherapy, hormonal therapy, and combination therapy. However, these have certain limitations. Therefore, it is encouraging to note that recent technological advancements have enabled researchers to explore modalities that not only cure cancer but also improve a patient's quality of life. Cancer reversion therapy is one such innovative therapeutic strategy that holds promise for cancer patients (Figure 1).

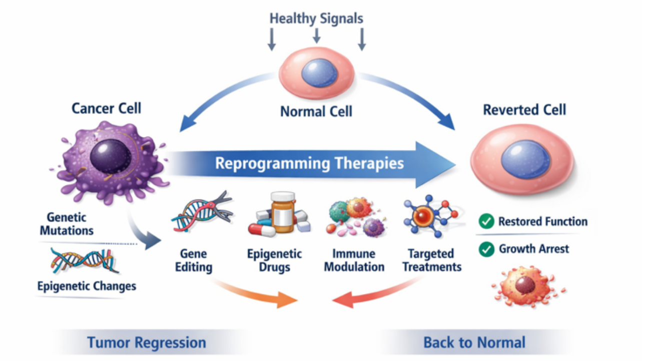

Figure 1: Basic principles of cancer reversion therapy

2. What is Cancer Reversion Therapy?

Cancer reversion therapy refers to the reversal of cancer cells into well-differentiated normal cells without killing them or other healthy cells in the body. A recent study has found that there is a critical transition

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period from normal cells to cancer cells, prior to full transformation. It has been found that during this transitory period, a cancer reversal molecular switch aids the reversion of the cancerization process[2].

3. Underlying Mechanism

During the transformation of a normal cell into a cancer cell, mutations occur at both the phenotypic and genetic levels. These involve (i) proto-oncogenes, (ii) tumor suppressor genes, (iii) apoptosis regulatory genes, and (iv) DNA repair genes. The normal functioning of these genes synchronizes the cell's response to external stimuli.

Initial studies on cancer reversion described *critical transition states*, involving so-called *attractors* that induced either normal cellular behavior (controlled proliferation/metabolic activity)[3] or abnormal behavior like a cancer cell (excessive uncontrolled proliferation/altered metabolic state). Attractors remain in highest concentrations in the attractor landscape, where the attractors of normal and cancer cells tend to remain in their stable behavior[3]. Any somatic mutations or drug exposure destabilize the attractor states and create the critical transition states[2]. This is the tipping point, where, even after the withdrawal of the causative factors, the cell remains in transition unless external stimuli drive the cell backwards to its previous normal state[3].

An external stimulus can induce a certain behavior inside the cell by acting on its complex molecular networks, referred to as the *input-output (IO) relationship* of the cell[4]. However, cancer cells, due to their mutations, have a distorted cellular response, ultimately resulting in uncontrolled proliferation. Thus, experiments based on digital simulation analysis were conducted to prove that restoration of normal IO relationships by molecular control in cancer cells is possible by reconnecting the molecular networks in such a way that would reverse the cell into its normal state[4].

4. Control of Differentiation Trajectories

1. In order to track molecules responsible for the transformation of a normally functioning cell into a cancerous one, the Boolean network inference and control (BENEIN)[5], was developed. It used the computational construction of gene regulatory networks (GRN) and formation of a map (single cell transcriptome data) from the available transcriptome data on human colon cells, where factors (or molecules) responsible for different functions of a cell and their correlations are sketched[6].
2. BENEIN tracked the *on* or *off* state of a molecule that is responsible for the functions in a normal cell and that of a cancer cell, whose activation (*on* state) or inhibition (*off* state) determined which molecule to target for bringing desired functionality or characteristics in a cell.
3. BENEIN is then used to create a twin model of the cell in question, called a pseudo-time trajectory, and is used to compare the pre- and post-transition states of a normal cell turning into a cancer cell.
4. Perturbation simulation analysis provided several molecules whose activation or inactivation cause either differentiation from stem cells or transformation into an undifferentiated cell.
5. Three master genes have been identified whose integrative *off* state causes the normal cell to maintain its usual stem cell differentiation into enterocytes, which also reverses the cancer cells into their pre-transformation normal characteristics. These master regulatory genes are (i) MYB (myeloblastosis oncogene), (ii) HDAC2 (histone deacetylase 2), and (iii) FOXA2 (forkhead box protein A2).
6. As a result, the colonic enterocyte markers KRT19 (keratin, type I cytoskeletal 19), KRT20 (keratin, type I cytoskeletal 20), and VDR (vitamin D receptor) increase in the colon cells that undergo reversion[5].

5. Reversion Switch[2]

1. This is a technology that automatically constructs GRN from single-cell RNA sequencing data of colon cancer cells, which are obtained from organoids of colon cancer patients. The technology is named REVERT (REVERse Transition), which is a novel system framework for identifying the reversion switches. These reversion switches are the transcription factors that could be the potential intervention targets for cancer reversion.
2. Using REVERT, a GRN model in the computer is formed that sketches the critical transition state of colorectal cancer, and distributes the attractors that represent normal and cancer cell phenotypes, by analyzing the attractor landscape.
3. Using the Boolean network model, a digital double of the transition state trajectory (the trajectory from normal to cancer cells) is made.
4. In the digital double, perturbation simulation analysis is carried out to quantify the attractor landscapes.
5. Changes made to the attractors are tracked. Finally, a series of transcription factors such as USP7 (ubiquitin-specific protease 7), APBB2 (amyloid beta precursor protein-binding family B member 2), and BDH1 (β-hydroxybutyrate dehydrogenase 1) are discovered, and their inhibition induces differentiation of colon cancer cells into normal colon cells.
6. Inhibitors of the transcription factor molecule USP7 were administered to colon cancer patients' organoids. This revealed that not only were the cancer-like characteristics of the cells suppressed, but also the normal cell-like characteristics of the colon cells were restored.

6. Why Colon Cancer Cells?

Most of the experiments were carried out on colon cancer cells. This might be due to the abundant volume of research data on these cells, since colorectal cancer is one of the most common cancers and is prevalent in both sexes.

7. Limitations

1. The initial studies have been conducted in mice and human organoids. Therefore, there is a need for testing in human cancer cells, and going forward, in animal models and eventually in clinical trials.
2. Heterogeneity of the tumors.
3. The experiments have been conducted only for colon cancer. Hence, testing in other types of cancer is warranted.
4. The research requires significant resources, expensive instrumentation and sustained funding.
5. The high treatment costs may limit accessibility and affordability for the masses.

8. Conclusion

If cancer reversion therapy is successful in clinical trials, it could lead to a paradigm shift in cancer therapy, alleviating the need for radical interventions, such as surgery or chemotherapy in many instances. Therefore, this new strategy has the potential for benefitting cancer patients worldwide.

Disclosure

The AI tool, ChatGPT (free version) was used to create the image presented in Figure 1.

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