 DOI: 10.18231/2395-6194.2017.0020

Membrane Marker Sensory Strategy- a neoteric concept

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Abstract

Cancer, the group of diseases is characterized by abnormal cell growth, thus the complications in physiological homeostasis. Although, not all tumors are cancerous, but after a certain time or biological events they may turn into cancer. In fact, it is always a risk to continue with any type of tumor. Over 100 cancers are affecting human are detected nowadays. Treatments belong to the types and stages of cancers along with the biological area. However, there is no single cancer therapy, which is free from side effects. Additionally, complications in cellular targeting and therapy-induced second cancer are also evident. Combination treatments are also used in some cancers, despite of the possibility of immunosuppressive and a bundle of unavoidable events. Otherwise, cancer treatment in advanced stages and metastasize are yet being considered as a problematic job. Therefore, scientists are always in search for a new and effective mode of cancer treatment, so that they may ensure less or even no side effects with a promising survival rate. In fact, the economy, safety, and effectiveness are the deemed query of both the patients and physicians. Among the others, the markers coming from the changed cell membrane of a cancerous cell may be a good target to ligand targeting, as these are the basic differentiating matter between two cell types (normal and cancer). In this hypothesis, the membrane marker sensory strategy is going to be introduced theoretically for the first time may be an alternative and effective mode of cancer treatment.

Keywords: Membrane marker; Novel strategy; Cancer therapy.

Introduction

The cancer cells are generally characterized by: acceleration of the cell cycle; genomic alterations; invasive growth; increased cell mobility; chemotaxis; secretion of lytic factors, etc. However, changes in the cell surface are also reported by these days. Till date, the commonly used therapeutic interventions in cancers are: surgery, chemotherapy, radio-therapy, targeted therapy and immunotherapy. The bone marrow and stem cell transplant, hyperthermia, photodynamic therapy, blood product donation and transfusion and laser treatment are also prescribed in some cases. It is noteworthy that, the cancer is a complicated disease in its networking and pathophysiological contributions. Therefore, the success of a particular cancer treatment depends on the proper diagnosis of its phase and implementation of concurrent effective management strategy(s). For an example, in earlier stage, surgery and immunotherapy are thought to be effective strategies in some cancers. However, an existence of any single cancerous cell may lead 'turn back' the situation. On this occasion, physicians are highly interested about a step-wise couple of therapies. For an example, surgery followed by radiation therapy. The latter one mainly works by imparting a reactive oxygen species (ROS)-mediated cell death phenomena. Thus, leads the question of insecurity of normal or non-cancerous cells from the ROS effects. In fact, the cells are always in contact with ROS coming from external and internal sources inside a biological system. Antioxidant (cytoprotective) agents can be used to avoid this situation, despite the 'antioxidative stresses' and 'pro-oxidative' effects are known.

Notably, in such a type of complicated disease, treatments functioning as multiple edged swords with beneficial and/or of use in a manner are highly appreciated. Chemotherapies compiled with two or more anticancer drugs are reported in this case. It is doubtless that, the targeting of drugs or other therapies in cancer is a complicated job. Otherwise, for a single cancer in different patients' may express different antigen against which a specific monoclonal antibody (immunotherapy) or cancer vaccine is targeted. Moreover, the mutation is a variable fact; therefore, the target antigens on the tumor cells at which the therapy is aimed also can be changed, thus leading less effectiveness or in effectivity of the therapy. In most cases, immune- or targeted therapies are directed towards following other therapies such as surgery, radio- or chemotherapy; which causes weakening and less response or non-responsive to the therapy. Otherwise, an early treatment with this kind of supplement is notably unnecessary, as it is not the same as those occurring from microbial attacking.

Patients' age and cancer stages are the two most important considerations in surgical treatment of cancer. Chance of infection, fatigue and needed for supportive other treatments such as – radio- and/or immune therapies are also seen on this occasion. Otherwise, the development of treatment-related side effects is the most common phenomena in chemotherapy. Nausea, vomiting, loss of appetite, constipation or diarrhea are frequently occurring in this

case. Fever, fatigue, alopecia, painful mouth sores and so forth are also reported. The chronic and acute side effects after radiotherapy mainly depend on the area of the body being treated, the dose given per day, the total dose given, the patient's general medical condition, and other treatments given at the same time. The rapidly dividing normal cells and the soft tissues are promptly susceptible to this kind of therapy. Skin irritation, salivary gland damage and fatigue are the most common side effects. Fibrosis, diarrhea, memory loss, infertility, second cancer (due to radiation exposure) are reported in radiation therapy. Laser therapy requires an expensive setup along with highly qualified surgeons. The shortness in the lasting of the effects is the major limitations of this therapy.[1] The common side effects in bone marrow and stem cell transplant therapy are occurring from the additional therapies needed such as – chemotherapy or radiotherapy. In most cases, infertility and the donor-derived disease are reported. Otherwise, a falling in white blood cell count is connected towards risk in infections and immunodeficiency phenomena. Low red blood cell count is often associated with the anemia and breathing complications, while low platelet levels lead to clot complication thus, the increasing bleeding time. Sickness, diarrhea, sore mouth and mouth ulcers, appetite and tiredness, sore eyes, jaundice, weight loss and skin rashes are the frequently occurring side effects in this occasion.[2]

Local hyperthermia is reported to cause pain at the site, infection, bleeding, blood clots, swelling, burns, blistering, and damage to the skin, muscles, and nerves near the treated area. However, the side effects depend on the type of hyperthermia used and application sites. Nausea, vomiting, diarrhea, complications in heart, blood vessels and other major organs are also demonstrated in this kind of cancer treatment strategy.[3] High tissue diffusive criteria and less effective in large tumor treatment are the two major limitations in photodynamic therapy. Skin and eye sensitivity, burns, swelling, pain, scarring in nearby healthy tissue, coughing, trouble swallowing, stomach pain, painful breathing, or shortness of breath are commonly reported in this kind of therapy.[1] Otherwise, infectious and non-infectious problems are reported with the transfusion of blood and blood products in cancer therapy. Acute transfusion reactions (e.g.- hemolytic reactions, allergic reactions, transfusion-related acute lung injury, febrile non-hemolytic transfusion reactions, transfusion-associated circulatory overload), delayed transfusion reactions (e.g.- transfusion-associated graft-versus-host disease) have frequently happened in this case.[4] In a word, a number of visible and invisible side effects are existed in a single anti-cancer therapy. Unfortunately, in most of the cases, those are unavoidable as well as un-treatable. Otherwise, still now most existing drugs inhibit only cancer cell proliferation other than the suppression of metastasis. There is no doubt that, the cancer metastasis has been often fatal.[5]

From the above discussion, it is clear that an effective cancer treatment strategy is always a dream to the physician as well as patients. After knowing the fact, in this writing, I am going to share a novel concept for an effective cancer treatment under the name 'membrane marker sensory strategy' or MMSS.

Hypothetical remark

A cancerous cell membrane is differentiated from the normal one by the loss of epithelial integrity, loss/decrease in polarity, loss of/alteration of junctional complexes and deterioration of basement membrane. Notably, the majority of the human cancers is derived from the epithelial tissues (more than 90%), and display loss of cell polarity. Among the four reported polarities (planar cell polarity, apical-basal polarity, front-rear polarity, and mitotic spindle polarity), the apical-basal polarity is thought to have an important role in both the initiation of tumorigenesis and in later stages of tumor development, favoring the progression of tumors from benign to malignant.[6] Cell polarity, which is defined as asymmetry in cell shape, organelle distribution and cell function, is essential in numerous biological processes, including cell growth, cell migration and invasion, molecular transport, and cell fate. Epithelial cell polarity is mainly regulated by three conserved polarity protein complexes, the Crumbs (CRB) complex, partitioning defective (PAR) complex and Scribble (SCRIB) complex. Apical-basal polarity maintenance mainly depends on cell polarity complexes and cell junction complexes, such as lateral adherens junctions (AJs), gap junctions, desmosomes, basal lamina hemidesmosomes, and apical tight junctions (TJs). AJs and TJs can interact with cell polarity complexes. The TJ is mainly composed of transmembrane proteins, including junctional adhesion molecules (JAMs), claudin and occludin, which combine with the actin cytoskeleton *via* the intracellular molecule ZO1, ZO2 or ZO3. The AJ isolates the apical membrane from the basolateral membrane. The AJ is mainly composed of transmembrane proteins, nectin and cadherin, which combine with the actin cytoskeleton *via* afadin and β-catenin, respectively.[7]

Otherwise, the epithelial tissues vary in form and function; despite of similar polarity in different tissues. In polarized epithelial cells, the apical surface is oriented towards the lumen or external environment. This side of the epithelial cell, which often has membrane protrusions (microvilli), takes care of the absorption, exchange and secretion of molecules and macromolecules. On the other hand, the lateral surfaces of the epithelial cells contact adjacent cells *via* specialized cell–cell junctions, namely tight junctions, adhesion junctions and desmosomes. The opposite side of the apical membrane, the basal surface anchors cells to a basement membrane, which is a thin (about 100

nm), dense sheet composed of a mesh-work of insoluble molecules, including laminin polymers, a cross-linked network of collagen IV fibrils, proteoglycans and glycoproteins.[8,9] In a recent study, in mammals, LKB1 (a serine-threonine kinase required for correct polarization) is reported to involve in maintaining or establishing polarity in mammary epithelia, pancreatic B cells, testes and neurons. It is also a tumor suppressor and can phosphorylate 13 other kinases, including AMPK, MARKs (PAR-1), NUAKs and MELK (PIG-1). To be mentioned that, the KB1-dependent phosphorylation of AMPK is important for energy regulation and cell growth involving mTOR signaling, and has been implicated in LKB1 tumor suppressor activity.[10] Although in study, phosphatidylserine, a lipid present at the outer membrane of the cancer cell was found to inhibit a pH-Low Insertion Peptide (pHLIP) in the basic pH,[11] but disaggregation of cancer cells along with their changes in membrane conformation is demonstrating the presence of some biomarkers surroundings as well as differentiating them from the normal cells. Those can be targeted as markers for therapeutic ligands, which may identify the cancer cells and eventually enter into the cancer cell (*via* complexation with them followed by an alteration of structural confirmation or direct protruding the cell membrane), thus imparting a cytotoxic, inhibitory effect on its growth and multiplication, and/or killing and scavenging from the physiological site. Although, the ROS for oxidative stress and inflammatory mediators are well-reported markers in cancer cells, but the targeting them to identify and enter into the cells is a new concept. In fact, the changed polarity of the membrane should be helpful for a modified non-polar ligand-marker complex or the marker sensed a non-polar moiety (ligand). A basic model has been shown as Fig. 1.

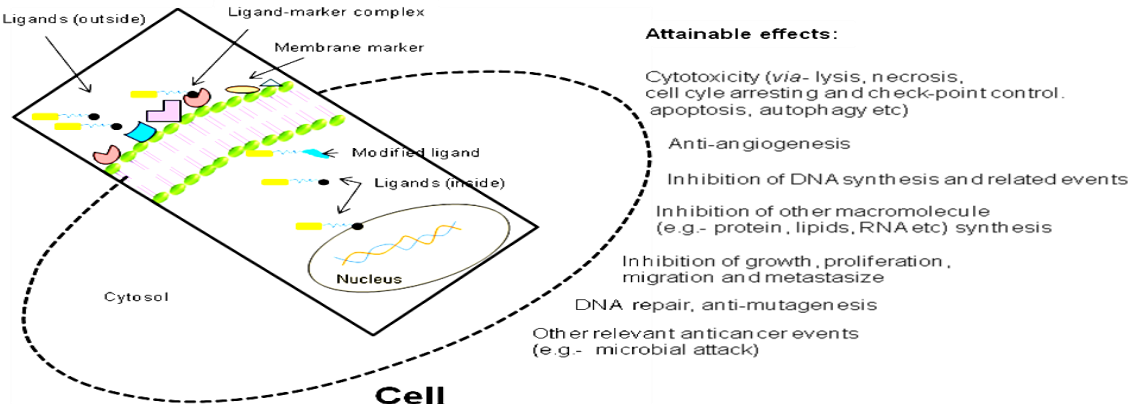

Fig. 1: Possible action pathways of the postulated MMSS in cancer treatment

Overview

Most of the drugs are polar in nature (except the steroids, those are from essential oils and a few). Thus, the decrease in membrane polarity will limit or inhibit to enter the polar ligands into the cells. In cancer, the cells are considered to be more oxygen and nutrient demanding as they are rapidly proliferating, plugging the core belief that the cells will pick up the drug molecule along with other nutrients. There is no doubt that, our daily consumed products (sources of nutrients) contain a number of substances having drug interference as well as drug-like activity. Notably, the normal cells also need those nutrients for their varieties of metabolic activities and they may have an affinity towards the same ligand (anticancer). In fact, the polarity question is a pale here, as the plasma membrane consists of a large amount of non-polar part. Otherwise, polar protein channels make the permeation of polar ligands easily through the membranes. Moreover, in a physiological system some cells are continuous in divisions such as blood cells and the sperm cells. Thus, leading a safety question to them also! In this way, any person in development stages will not be safe to the anticancer therapy, especially with the anticancer drugs.

One more thing should be clear that, in rapid divisional phases, cancer cells utilizing more nutrients and oxygen will undergo to produce more toxic metabolites also. Among them, the number of polar metabolites is remarkable. The decreased polarity of the cell membrane will reduce their diffusion through the non-polar membrane. Thus the existence of the cell will be more difficult, due to its self toxic effect (cyto-toxico burst)! On the other hand, the cancer cells will deprive the normal cells from oxygen and nutrients, especially those are living with/aside them. The latter event may be linked to the cancer cells-induced chronic detrimental effects upon the normal cells. If it continues, the number of cancerous cells will be increased day by day. In addition to it, the loss of junctional ligations among the cancerous cells along with the increasing demand for nutrients and oxygen within the cancer cell population may be plugged with the metastasis phenomena. This is due to their survival

question rather than the intenstion to cause harm to the host. On this occasion, a treatment mediated 'second cancer' is a possible manifestation.

It is doubtless that, now we have a number of cancer detection systems. However, the targeted therapies in a particular cancer are still complicated, especially the therapies compiled with radiation and chemotherapeutic agents. After surgery, these are thought to be the potential mode of therapies. The strategies used in cancer including, immuno-, blood or blood product transfusion, cell or tissue culture, laser and so on having some visible and non-visible acute and chronic side effects also some noteworthy facts in cancer treatments. However, radiation-induced ROS effects and chemotherapeutic agents-mediated ROS and other events are always creating challenges in cancer therapy. Fortunately, researches and some practical implementation reports say that, drug targeting is possible in cancers; despite of ensuring a complete security of the normal cells and events may happen after treatment. In every killing effect with a particular cancer therapy, the reduction of the number of cells occurs. It seems not only we are going to be free from cancerous events, but also from a reduced cellular function of the specific group of cells called tissue. In a biological system, the total coordination among the tissues (tissue activity) is crucial for homeostasis. Therefore, the reduction of the number of some specialized cells, such as cardiac, nephritic and neurotic, especially in the late stages of life is a burning question, as the reduction of activity, mal or wrong formation of metabolic products, including ROS as well as a reduction of sensitivity towards the internal and external markers happen in this context. Otherwise, the permeability of the biological barriers is unique in their nature. Thus, asking an appropriate and intellectual molecular targeting of a therapeutic agent, this is quite difficult to attain *via* any route of administration. On the other hand, drug insertion by using some special device is always challenging, expert needing, costly and time consuming matter. In a word, the complexity and connections of biological systems and cancers, side effects and limitations of the therapies and relevant other factors are always asking simple solution in this terrible disease.

The important features of the offered hypothesis (MMSS) are: (I) molecular targeting; (II) implacability in various stages in cancer; (III) avoidance of additional targeting; (IV) avoidance of cell escaping and 'turn back situation'; (V) avoidance of combinatorial and step-wise treatment strategies; (VI) chance of multi-edged action pathways; (VII) escaping normal cells asides the cancer cells (as complete different membrane biomarkers are targeted); (VIII) chance of the development of ligands with variability in targets; (IX) chance of the development of physiologically compatible ligands; (X) chance of free hand selection of dose (as the ligand is specific in its target); and (XI) economy, thus the replacing ability of currently using expensive strategies. It seems the MMSS may be an effectual and novel cancer treatment strategy ever told. However, it is still a theoretical strategy and yet to be established.

Conclusion

The figure out novel markers differentiating the membrane of a cancer cell and a normal one is considered to be a challenge. Otherwise, the cellular conformation in different tissues in a biological system is the hallmark in its pathophysiology and the causes of cancer are numerous. However, the varieties in mode of action, reproducibility, greater chance of action pathway modification, ability in self-targeting, and many other features offering for a particular ligand in MMSS may open an optimistic door in the cancer treatment. The action is totally featured with the membrane marker sensed ligand's chemico-biological interaction characteristics.

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