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Beta receptor proliferation in alkaline medium and the consequent effects on tumour and malignant cells

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Abstract
Introduction: Cancer is an abnormal state in which uncontrolled proliferation of one or more cell populations interferes with normal biological functioning. The paper describes the involvement of different factors in order to maintain bodily homeostasis through cell-surface specific receptors and specifically highlights the insights of Beta Receptor Proliferation in Alkaline Medium and the Consequent Effects on Tumour and Malignant Cells.
Hypothesis and Relevant Analysis: Since, normal homeostasis requires intricately balanced interactions between cells and the network of secreted proteins known as the extra cellular matrix, generation of disease results due to disruption in the balance between the cells and the extra cellular matrix. As, such cooperative interactions involve numerous cytokines acting through specific cell-surface receptors, in the present paper we have studied a lot of cases of breast cancers, gastric cancer, prostate cancer, several gynecologic malignant cases and analyzed especially the proliferation of beta receptors in alkaline medium and the consequent effects on tumour and malignant cells.
Conclusions: From the in depth studies and analysis we found that, proliferation of tumour and malignant cells is favoured in acidic medium and also, proliferation of alpha receptors are enhanced during tumour generation as well as malignancy. Inhibition of such proliferation of malignant cells are found to be associated with the proliferation of beta receptors in alkaline medium.

Keywords: Cell-surface receptors, Beta receptor proliferation, Homeostasis, Malignancy, Agonist-antagonist.

1. Introduction
In human tissues, normal homeostasis requires intricately balanced interactions between cells and the network of secreted proteins known as the extra cellular matrix. These cooperative interactions involve numerous cytokines acting through specific cell-surface receptors. When the balance between the cells and the extra cellular matrix is perturbed, disease can result. This is clearly evident in the interactions mediated by the cytokine transforming growth factor ß (TGF-ß) [1, 2].

Hypothesis and Relevant Analysis
TGF-ß is a member of a family of dimeric polypeptide growth factors that includes bone morphogenic proteins and activins. All of these growth factors share a cluster of conserved cysteine residues that form a common cysteine knot structure held together by intramolecular disulfide bonds [1]. Virtually every cell in the body, including epithelial, endothelial, hematopoietic, neuronal, and connective-tissue cells, produces TGF-ß and has receptors for it. TGF-ß regulates the proliferation and differentiation of cells, embryonic development, wound healing, and angiogenesis. The essential role of the TGF-ß signaling pathway in these processes has been demonstrated by targeted deletion of the genes encoding members of this pathway in mice.
Increases or decreases in the production of TGF-ß have been linked to numerous disease states, including atherosclerosis and fibrotic disease of the kidney, liver, and lung. Mutations in the genes for TGF-ß, its receptors, or intracellular signaling molecules associated with TGF-ß are also important in the pathogenesis of disease, particularly cancer and hereditary hemorrhagic telangiectasia. This paper will discuss the mechanisms by which TGF-ß [51] mediates its cellular functions, focusing on its role in disease, particularly diseases in which genetic mutations in the TGF-ß pathway have been documented.

Results from investigation of cancer cell and tumor physiology and metabolism using non-invasive imaging and spectroscopic methods [1A, 2A] opened a new area of knowledge that are important to the basic mechanisms of carcinogenesis, as well as to cancer diagnosis and treatment. Cancer is often characterized as a genetic disease, since it invariably results from genomic alterations or mutations. However, only 20% of cancers are clearly heritable, meaning that the majority of cancers have environmental triggers. It has been found that the environmental (interstitial) pH of tumors is quite acidic. This was determined using Nuclear Magnetic Resonance Spectroscopy (MRS) of human tumors grown in SCID mice. Using magnetic resonance imaging (MRI), a relationship between angiogenesis, the metabolism and low pH [3, 5] in tumors has been found. This acidic pH affects therapeutic efficacy and may impact on carcinogenesis itself [5]. A major research project focused on improving measurement of acid pH by MRS and defining the impact of acid pH on chemotherapy. Acidic pH makes tumors physiologically resistant to weakly basic chemotherapeutic drugs [3], such as doxorubicin (Adriamycin). Raising the tumor pH reverses this resistance. It has also shown that this acid pH induces tumor cells to become more invasive [5, 8], which is a hallmark of malignancy [13-16]. Transfection of metastatic cells with nm23, which inhibits metastasis, has a significant impact on cellular lipid metabolism and cellular pH homeostasis [18-24]. Changes in lipid metabolism is an important diagnostic marker for cancer progression.

Cell pH is regulated by three distinct families of transporters: Na^+/H^+ exchange [12, 36], bicarbonate transport and proton ATPases. A significant number of human tumor cells express Vacuolar-type H(+)-ATPases (V-ATPase) in their plasma membranes. Experimental evidences are in support of the subunits of this pump from human cDNA libraries and are using expression clones to raise antibodies against extra cellular epitopes of this pump. Research using antibodies which recognize these extracellular epitopes suggests that these ATPases are constantly and rapidly turned over between intracellular organelles and the cell surface [33]. This activity could have a significant effect on resistance of tumor cells to weakly basic chemotherapeutic drugs, such as adriamycin (doxorubicin) or mitoxantrone.

Chemotherapy is a sort of treatment involving the use of drugs to kill cancer cells. Cancer chemotherapy may consist of single drug or combinations of drugs. Chemotherapy is different from surgery or radiation therapy in that the cancer-fighting drugs circulate in the blood to parts of the body where the cancer may have spread and can kill or eliminate cancers cells at sites great distances from the original cancer. As a result, chemotherapy is considered a systemic treatment.

Catecholamine interactions are very important in terms of focusing drug-receptor interactions in various stages as well as status in human body [58].

Catecholamines are excitatory or inhibitory neurotransmitters or hormonal agents. The catecholamine neuro-hormones are *epinephrine, norepinephrine, dopamine and serotonin.*

Adrenergic receptors or Adrenoceptors are transmembrane glycoproteins of plasma membrane and mediate the cellular effects of catecholamines. Those receptors are classified on the basis of their pharmacological antagonists. Three types or subfamilies of adrenergic receptors have been identified: the *alpha*-1, *alpha*-2 and *beta*. Within each of these subfamilies are receptor subtypes, including the subtypes of *alpha*-2 adrenergic receptors: *alpha*-2A, -2B and -2C. β-Adrenergic receptors are of two types(β_1 and β_2 receptors).

At physiological concentrations, noradrenaline binds to and mainly activates the α- receptors; whereas adrenaline binds to both α and β receptors and the tissue response to it depends on their relative concentrations on the target cell membrane as well as their relative affinities for adrenaline.

Binding of catecholamines to β_1 and β_2 receptors activates adenylate cyclase in the target cell membrane. Adenylate cyclase activity increases the intracellular concentration of Cyclic AMP(cAMP). The latter allosterically activates specific protein kinases (protein kinase A) which phosphorylates specific proteins or enzymes, activating some of them and inactivating others. Basically this leads to the cellular responses. Chronic rises in blood catecholamines down-regulate the numbers of β-receptors on the target cells, and also reduce the activity of the remaining β receptors by uncoupling them from adenylate cyclase. Thyroid hormones increase the β effects of catecholamines by up-regulating the number of β-adrenergic receptors and facilitating their coupling with adenylate cyclase.

Binding of catecholamines to α_2 receptors inhibits the adenylate cyclase-cAMP system to reduce the intracellular cAMP concentration; this leads to the tissue responses in α_2 effects.

Binding of catecholamines to the $\alpha_1$receptors activates in contrast the phospholipase C-phosphoinositol system to enhance the formation of inositol 1,4,5-triphosphate and diacylglycerol and to raise the intracellular concentration of Ca^{++}; these may act as the second messengers to produce tissue responses for α_1 effects.

The expression of these receptors is not static and can change with disease, aging or therapeutic treatment. Alteration of receptor spectral density can occur at any of the steps from gene transcription to degradation of the receptor protein itself. Continued agonist stimulation of a receptor population often causes a rapid reduction in response to the agonist [27], a phenomenon known as desensitization. Short-term desensitization is characterized as a rapid (minutes) and reversible uncoupling of the receptor-G protein complex mediated by receptor phosphorylation. This is followed by sequestration and internalization of receptors from the cell surface. Receptors are not lost during short-term desensitization because removal of agonist rapidly restores receptor function. Down-regulation[28, 30], on the other hand, is defined as a decrease in receptor density and displays a much longer time course (hours) which is thought to result from an actual loss of receptors. Removal of agonist will allow recovery of receptor density, but this recovery takes longer, requiring synthesis of new receptors in most cases.

Long term exposure to agonist down-regulates receptor expression for many G-protein coupled receptors. What happens is that, The ligand molecules are sequentially missing different functional groups [Ref: Pubmed: PMID: 11306720]. An interesting feature is that, whenever alpha adrenergic receptors exhibit agonist mode of action [31, 32], at the same time beta adrenergic receptors exhibit antagonistic action. At this, a ligand relaxation [39] is formed paying regards to the binding of those receptors to G-protein.[28, 29, 30, 46].

In fact, G-protein coupled receptors (GPCRs) constitute the largest class of cell surface signaling molecules in eukaryotes and in some prokaryotes. By activating their cognate

heterotrimeric guanosine triphosphate (GTP) binding proteins(G-proteins), GPCRs transduce stimulatory or inhibitory signals for a wide array of endogenous hormones and neurotransmitters, ambient physical and chemical stimuli, as well as exogenous therapeutic agents. Beta adrenergic receptors (βARs) are archetypical members of the GPCR superfamily. There are, at least, two types of β_1AR and β_2AR present in most of our cells. Whereas both βAR subtypes can stimulate the classic G_s-adenylyl cyclase-cAMP-protein kinase A(PKA) signaling cascade [33], β_2AR can activate bifurcated signaling pathways through G_s and G_i proteins. Because of their distinct G-protein coupling, these βAR subtypes fulfill distinct [34, 35], sometimes even opposite, physiological and pathological roles.

On the other hand we have also found that, though the intracellular pH is alkaline during chemotherapy, β_1AR is not capable to support cellular survival. In sharp contrast, β_2AR in the similar alkaline medium helps/ favours cellular survival. Such phenomenon virtually takes place that due to ligand relaxation of β_1AR and β_2AR to G-protein [39, 47]. In fact, both the beta adrenergic receptors cannot bind together at the same time to the G-protein. Rather, once coupling of β_1AR and G-protein dominates, the binding of the second one remains as recessive. On the other hand, when the coupling of β_2AR –G proteins dominates, the other remains in relaxed mode. Naturally, in our analysis, it has been shown that, administration of β_2-G protein coupling agent is favouring normal cell survival [38, 48] in favourable alkaline medium.

We want to quote a comment of Dr. OTTO WARBURG, (*Two Time NOBEL PRIZE Winner*), "The great advantage of knowing the prime cause of a disease is that it can then be attacked logically and over a broad front. This is particularly important in the case of cancer, with its numerous secondary and remote causes, and because it is often stated that in man alone there are over one hundred well-known and quite different kinds of cancer, usually with the implication that therefore we will have to find one or several hundred bases for prevention and treatment, and usually without any realization that this need not necessarily be the case now that we know that all cancers studied have a characteristic metabolism in common, a prime cause." Paying regards to his opinion, apart from our study on the consequent events of beta receptor proliferation & alkaline medium associated with tumour and cancer cells, we also interested to cultivate our study to find out, if, there are some Naturally occurring factors, which can impart their important role in favour of beta receptor proliferation, generation of alkaline medium and thereby inhibition of proliferation of tumour as well as cancer cells [53, 55].

During cultivation of involvement of different factors associated with tumour as well as cancer cells, we were very much careful to study in terms of their cause of genesis and also to the factors that are involved to provide their inhibitory actions to those effected cells in comparison to that of healthy cells, it was found that, apart from synthetic drugs and traditional treatment concepts, there are several factors, that are much efficient in order to impart their role to inhibit the proliferation of tumour as well as cancer cells. Though, those factors are belonging to the group of Alternative and Complementary Systems of medicine / treatment, we have cultivated the route of their involvement and tried to focus the insight of their participation and sequential steps in order to inhibit or arrest the proliferation of tumour and cancer cells. At a pH slightly above 7.4 cancer cells become dormant and at pH 8.5 cancer cells will die while healthy cells will live[54,55]. This has given rise to a variety of treatments based on increasing the alkalinity of the tissues such as vegetarian diet, the drinking of fresh fruit and vegetable juices, and dietary supplementation with alkaline minerals such as calcium, potassium, magnesium, cesium and rubidium [53,57] are found as much effective in fighting cancer. We also found that, oxygen plays a vital role in favour of inhibition of cancer in our body. Excessive oxygenation enhances alkaline environment in our tissues. Dr. Szent-Gyorgy won the Nobel prize in 1937 for discovering that essential fatty acids combined with sulphur-rich proteins (such as those found in diary products) increases oxygenation of the body. Dr. Budwig applied this discovery in clinical trials by feeding cancer patients a mixture of 3-6 Tbsps [56].

In Holland the vegetarian diet promoted by Dr. Moerman has been recognized by the government as a legitimate treatment for cancer. Results indicate that Dr. Moerman's diet is more effective than standard cancer treatments (Jochems, 1990) [57].

2. Conclusions

In the present paper, it is found that, β-receptor proliferation in alkaline medium appears to be extremely important in terms of treatment of cancer cells paying regards to the receptor agonist and antagonist play game in vivo. This is as because, α- receptor is found to be favourable in favour of proliferation of cancer cells which is also supported immensely by acidic medium. And, at the same time, proliferation of β-receptor in many cases inhibits the growth of cancer cells, which is also found to be enhanced in alkaline medium. According to our analytical findings, the agonist and antagonist features of different types of receptors may provide a crucial clue as well as solution in order to reduce the failure of growth regulation of cancer cells, and also to those cells, suffering from any sort of trigger that may lead or turn them in tumour or malignant stage. Several Naturally occurring materials such as elevation of oxygen levels, fresh fruit and vegetable juices, inclusion of different alkaline minerals combination in the diet may also impart a vital role in the proliferation of beta receptors and in turn inhibiting the growth of tumour and cancer cells.

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Author's Contribution

Dr. Anjana Mazumdar, (M.D.S) is the Professor of the Department of Oral Pathology in Dr. R. Ahmed Govt. Dental College, Kolkata, India. She furnished the innovative idea in the present paper and provided comprehensive guidance to the total research work in favour of this hypothesis in order to achieve a positive output. Partha Majumder is Gold Medalist in Human Physiology, having area of cultivation in recent Biomedical research and former Head of the

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