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Electrical-Pulse-Mediated Cancer Therapy

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Every 13 minutes (approximately 40,000 per year), a mother, an aunt, a sister, a wife - a woman dies due to breast cancer in the US and over 400,000 women worldwide. Every 1.5minutes there is a cancer death in the US (about 300,000 per year). It is estimated that 12.7 Million cases and 7.6 Million deaths to have occurred in 2008 worldwide and it is only increasing. Once cancer is a disease of the affluent, industrialized western world, now, cancer is everywhere-in India, China, Korean, Africa and Egypt. There are over one million cancer cases in India. There is a pressing need for alternate physical therapies for unresponsive cancers to the conventional modalities of treatments including surgery, chemo therapy, radio therapy, and immunotherapy. The poor response rates, 10% to 54% of many commonly prescribed breast cancer drugs, such as Doxorubicin, Paclitaxel, and Tamoxifen also contribute to morbidity and mortality of cancer.

Thus patients with in-operable, recurrent, chemo-resistant tumors need affordable, alternate treatments. Towards this end, electroporation or electropermeabilization (EP) is a viable physical technique wherein high intensity, short duration (100 microseconds (μs)) pulses are applied to temporarily open up pores in the plasma membrane of cells to allow transport of therapeutic materials including drugs, antibodies and genes (DNA) which otherwise are impermeable. Since the application of pulses is only for a very short duration, the cell membranes eventually reseal and make the drug molecules to act. A low dose of the chemo drug is injected intratumorally or intravenously, a few minutes before the application of the pulses. When used to deliver chemo drugs, this technique is called Electro-Chemo-Therapy (ECT). Its success has been attested by the various clinical trails and ongoing treatments for extreme cases of melanomas, sarcomas, and other skin cancers including head and neck cancers. When surgery, radio and chemotherapies didn't work, patients suffering from chest wall breast carcinoma benefitted using ECT. Thus, electrical pulse-mediated drug delivery is an attractive option where conventional treatments do not work for the patients.

Understanding the molecular and cellular events involved in tumor formation, progression, metastasis, and drug binding is crucial to the development of innovative therapy for cancer patients. The human body could be considered as a composite conductor comprising a number of spatially distributed tissues/cells with differing electrical properties. Unlike metallic conductors, electrical conduction within biological cells is due to ions in which electrostatics also plays a major role in DNA's function, drug binding and cellular proliferation.

Electrostatic interactions are critical for protein structure and functions. The electrostatic potential, governed by the Poisson-Boltzmann equation is a function of all species of ions present in the solution, volume concentration of the species in the bulk, charge of the species and dielectric permittivity of the solvent and the temperature. Recently, it was shown that by considering the dynamic solvent microstructure (especially the Debye polarization of water molecules), sophisticated electrostatic effects at the protein-solvent interface could be revealed. Thus, Cellular electrostatic interactions are also related to cancer and its treatment as dictated or directed by ribosomes. They catalyze the assembly of amino acids into proteins using messenger RNA as a template. This process is called translation. Ribosomes are central to protein synthesis machinery and thus are target for several pharmaceuticals. The activity of ribosomes is dependent upon their appropriate three dimensional conformation which is influenced by electrostatic interactions between RNA and protein components. The functioning of ribosomes, and subsequent expression of distinct proteins, plays a major role in normal growth, development and disease pathogenesis. Thus, electrostatic interactions responsible for regulating ribosome efficiency can have a profound impact on diseases such as cancer, and its drug binding to DNA.

Ribosome systems have electrostatic properties which will provide information on translation and the rational design of novel antibiotics, for cancer and other diseases. Several ribosomal proteins are activated in a variety of tumors. Several tumor suppressors and proto-oncogenes have been found either to affect the formation of the mature ribosome or to regulate the activity of proteins known as translation factors. Disruption in one or more of the steps that control protein biosynthesis has been associated with alterations in the cell cycle and regulation of cell growth. Therefore, certain tumor suppressors and proto-oncogenes might regulate malignant progression by altering the protein synthesis machinery. Many studies have correlated deregulation of protein biosynthesis with cancer. Thus, the ability to determine the contribution of electrostatics to the forces and energies of biological systems should help better cure for cancer using electrical pulses and the devise of better drugs, including nanomedicine, with fewer side effects.

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