Science INSIGHTS®
Journal of The Bonoi Academy of Science & Education

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Science Insights 2015; 11(3):346-354
Doi: http://dx.doi.org/10.15354/si.14.re102
Science Insights is published by The Bonoi Academy of Science & Education, Chapel Hill, NC 27510, USA

p-ISSN: 2372-8191
e-ISSN: 2329-5856
DOI: 10.15354/issn.2329-5856

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Historical and Practical Perspective of the Unique Surface Electrical Properties of Cancer Cells

Dong Wang,*,Δ Wen-ying Wang,† Zheng Cui,‡ Dong-lu Shi ¶

SUMMARY The fact that cancer cells have abnormal surface electrical charges has been discovered for more than half a century and yet it still has not been understood well despite of enormous efforts in cancerous research. Due to the lack of effective tools for the real-time measurement of electrical properties of individual live intact cells, researches for cancer cellular electricity has been plagued with much less understanding than other cellular signaling mechanisms. We herein review the major historic events of discovering the abnormal surface electrical properties of cancer cells. Although it is still difficult to fully understand this unique property of cancer cells, some applications using the unique surface electrical property of cancer cells, such as the polycation functionalized nanomaterials as the targeted anti-cancer drug delivery system and the utilization of the positively charged host defense peptides as universal anti-cancer drugs, are also reviewed. With the appearance of innovative techniques, the electrical properties of cancer cell surface can attract sufficient efforts to further understand their underlying mechanisms and implications in the clinical settings for diagnosing and treating cancer.■

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Received: 17 December, 2014
Revised: 22 December, 2014
Accepted: 05 January, 2015

Doi: 10.15354/si.14.re102

SCIENCE INSIGHTS 2015; 11(3):346-354

How to Cite This Paper: Wang D, Wang W, Cui Z, Shi D. Historical and practical perspective of the unique surface electrical properties of cancer cells. Science Insights 2015;11(3):346-354. DOI: http://dx.doi.org/10.15354/si.14.re102.

Keywords: Cancer cells – Surface charge – Electrical property – Host defense peptides – Cationic liposome

ELECTRIC PROCESS is the basis of the biological process, and also undergoes the strong association with the health and different types of diseases (1). Albert Szent-Györgyi, the Nobel Prize laureate in Physiology and Medicine in 1937, indicated in his book *Bioelectronics* that biochemical explanations alone fail to explain the role of electricity in cellular regulation (2). He believed that the cells possess electrical mechanisms and use electricity to regulate and control the transduction of chemical energy and other life processes. Electromagnetic fields have information and communication roles in

that they are employed by living organisms as information conveyors from the environment to the organism, within the organism and among organisms (3). The importance of the widespread use of electricity in biological function cannot be overstated. All the important biological functions, such as the transduction of information from the environment to the organism, within the organism and among organisms, the regulation of cellular volume, the transport of metabolites, the control of the cell cycle, cell proliferation, cell migration and tissue regeneration etc.(4) are intimately linked to the flow of bioelectric signals. Normal cells possess the ability to communicate information inside themselves and between other cells through a series of well-regulated biological electronic circuits and wireless communication mechanisms. Cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to unregulated balance of cell proliferation and cell death and ultimately evolving into a population of cells that can invade tissues and metastasize to distant sites, causing significant morbidity and, if untreated, death of the host (5). When cancer arises cancer cells are no longer regulated by the normal control mechanisms, the bioelectric signals inside and between cancer cells also become abnormal. Merrill Garnett has reported that all cancer cells have abnormal electron transfer systems while normal cell development involves normal energy flows (6).

The Historic Perspective of Discovering the Abnormal Electrical Properties of Cancer Cells

Two distinguishing biological characteristics of malignant tumors are their ability to invade adjacent normal tissues and their ability to produce secondary tumors in distant parts of the body (7). There is evidence to indicate that the cells of normal tissues and also the cells of benign tumors are so firmly attached to one another that they are unable to escape. In contrast, the cells of malignant tumors are often found in the body free from the parent tumor (7). The reason that the cancer cells become free movement is considered as their greatly reduced adhesiveness.

Back to 1940s, Coman and colleagues (8-10) seem the pioneer researches to observe changes in the mutual adhesiveness properties of tumorous cells. While he was making attempts to separate single cancer cells from each other, Coman noticed something peculiar about cancer cells: they were much easier to be separated from each other than their normal cell counterparts with micromanipulator. When the forces of the separating needle to pull apart two cells were measured and compared, the average forces to pull apart cancer cells were 3 times smaller than that needed for separating normal cells. He initially noticed this phenomenon in the carcinomas from the lip. Then similar observations were made in cervical squamous cell carcinomas and glandular adenocarcinomas (11). It was theorized at that time that such a cellular behavior might be responsible for cancer cells to break free from original tumor and metastasize to distant sites. Later on, Abercrombie and Heaysman also noticed that, when cultured on culture plates, the growth of normal cells stopped if the cells began to touch each other, a phenomenon termed as contact inhibition. As result, normal cells could only grow as a monolayer. However, sarcoma cells seemed to have lost such a contact inhibition and grew on top of each other as three-dimensional aggregates (12, 13). It was thought that loss of contact inhibition was also due to a loss of cell adhesion, and cancer cells obtained some forces to propel themselves from each other (14). After that it was reasoned that the strong adhesiveness could only be achieved among similar cells with minimal amount of surface charges. A loss of cell adhesion could only suggest that cancer cells might have gained excess surface charges (15, 16). This excess charge results in a greater electrostatic repulsive force between cells and disrupts the attractive force of contacting membranes that is caused by other reactions (17). In 1950's, in order to test the theory that cancerous cells might have gained surface charges, Ambrose et al. used cell electrophoresis technique to evaluate the cancer cells (18). They noticed that in comparison to normal cells with no movement or with slight movement towards the anode, cancer cells were indeed moving towards the anode, indicating that they are negatively charged on their surface. This might be the first demonstration for the negative charges on the cancer cells. This observation was also extended into several other cancer lines from kidneys and livers and as well as fresh primary cancer cells (19-21). All the above investigations give evidence that the lessened mutual adhesiveness is characteristic of carcinoma cells generally, and the reduction in cohesive strength between carcinoma cells might be attributed to a considerably excess negative electrical charge on membrane surfaces than the homologous normal cells that reflect structural-functional changes.

In later years, Ambrose et al. expand the studies with additional techniques to detect the surface charges of cancer cells (22). In that research, on examination of the cells microscopically 90 seconds after mixing with polyethylene imine (PEI) at very low concentrations, Ehrlich ascites cells were found to be almost completely agglutinated into clumps of varying size. Some aggregates contained up to 50 cells. In the control samples of untreated cells, groups from two to four cells in contact were observed, but no group of larger size could be seen. Comparison has been made with red blood cells and spleen cells. By mixing the PEI with the red blood cells, these cells did not clump or form rouleaux even up to 3 hours after mounting and showed a normal appearance. PEI agglutinated the tumor cells selectively, having less affinity both for red blood cells and spleen cells. It was reported that erythrocytes carry a high negative surface charge

like tumor cells, but these results suggest that, at least in this transplanted tumor, the distribution of charges on the cell surface differs from that of the erythrocytes. A similar agglutinating effect was observed with another positively charged polyelectrolyte, polyvinyl pyridinium bromide. However, when the experiment was carried out using polyglutamic acid or heparin, two typical negatively charged polyelectrolytes, no agglutination was observed in cell suspensions. Also, there was no visible change occurred when the cells were incubated with the nonelectrolyte polymer, polysarcosine. Besides, the positively charged polyelectrolytes also displayed remarkable antitumor activity in vivo when administered intraperitoneally (i.p.) to treat 1-day intraperitoneal Ehrlich ascites. Therefore, binding to positively charged polymers suggested once again that there was a strong negative charge on the surface of cancer cells but not on normal cells.

In addition to the aggregation effect, the anticancer effects of several positively charged materials were also tested. Polycations like polyethyleneimine, polyvinylamine, polypropyleneimine, polylysine and diethylaminoethyl-Dextran, positively charged colloidal ferric oxide particles and cationized ferritin all showed significant anticancer effects in both cultured cells and modeled cancer animals (23-30).

The Reason of the Enhanced Surface Negative Charge of Cancer Cells

The popular speculations about the cause of obviously more negative surface charge on cancer cells than that of normal cells is the significant gain of anionic moieties on the outside of cancer cell plasma membrane, such as the sialic acid moiety of immobile glycolipids and glycoprotein or the serine head group of phosphatidylserine of the lipid bilayer (31-36). Forrester et al. (33) demonstrated that sialic acid anions are responsible for a major portion of the surface negative charges on erythrocytes and various tumor cells. Analyses of several types of human cancer tissues revealed that the area of malignancy contained almost twice as much sialic acid as the normal areas of the same tissues (34). BMAP-27 and BMAP-28, cationic host defense peptides from the cathelicidin family, exhibited lower activity on cancer cells when sialic acid had been cleaved off (36), which suggested that sialic acid contributes to the net negative charge on the cell membrane and the outside negative charge seems to act as an initial interaction site for the peptides.

However, such proposition about the overexpression of sialic acid moiety and phosphatidylserine on the surface of cancer cells are still controversial. First, exposure of the negatively charged phosphatidylserine on the cell surface mainly results from the loss of asymmetry occurs not only during malignant transformation, but also at the time of cell injury, apoptosis, necrosis and cell activation (37-39). There is also an increase in sialic acid-rich glycoproteins in inflammatory diseases (40, 41). There have not been consistent results showing that much more phosphatidylserine or sialic acid on the surface of cancer cells than normal cells. Second, some reports showed that enzymatic removal of sialic acids from the outer membrane of cancer cells could not affect the electrophoretic mobility of cancer cells (42-45), suggesting the immobile anionic groups contribute very little to the cellular surface charges. Third, in comparison to the massive amount of mobile ions that are known to be responsible for the electrical properties of surface membranes, the number of immobile ionic groups is just too small to be useful. The research field of bioelectricity in cells has been at difficult cross-points of biology, physics, and chemistry. Because of the lack of tools for such measurement in mammalian cells, the research for cancer cellular electricity has been plagued with much less understanding than other signaling mechanisms for cells.

Applications Based On the Unique Surface Charge Property of Cancer Cells

Although it is still difficult to fully understand the unique charge property of the cancer cell, the negatively charged cancer cell surface has been paid much attention to for several decades, especially in the application of cationic polymers or polycation functionalized nanomaterials as the targeted anti-cancer drug carriers in drug delivery system.

Polylysine

Polylysine (ε-poly-L-lysine, EPL), which belongs to the group of cationic polymers, is typically produced as a homo-polypeptide of approximately 25-30 L-lysine residues. Polylysine showed unique antimicrobial activity against yeast, fungi, Gram-positive and -negative bacteria at a low concentration while have no cytotoxicity effect on healthy eukaryotes even at a high concentration (46). The proposed antimicrobial mechanism is that cationic polylysine are able to absorb electrostatically to negatively charged cell surfaces of microorganisms, followed by a stripping of the outer membrane, then abnormal distribution of the cytoplasm, and finally cell death (47).

By incubation of the tumor cells with polylysine or lysine-rich histone fractions, Shah et al. observed the obviously inhibitory effect on the growth of transplantable mouse mammary tumors (48). The investigation about the effects of polylysine on the electrophoretic mobility (zeta potential) of saline-washed Ehrlich ascites tumor cells have shown that the polylysine change the net negative charge of the tumor cell membrane to zero or high positive values (27). It could be reasonably suggested that the negative surface charge of the tumor cells play an important role in its highly invasive properties and the inhibition effect of

polylysine to the growth of tumor. Afterwards, Arnold et al. (49) have discovered that White Swiss mice show nearly a 100% remission from subsequent tumor growth when given optimal doses of polylysine i.p. after inoculating with Ehrlich ascites cells. The vitro cell viability study indicates that polylysine has a high affinity and a marked concentration dependent cytotoxicity for Hela cells (49). Studies with a fluorescent polylysine derivative also demonstrated that the largest amount of polylysine derivative binds to the lipoprotein surface of Ehrlich ascites tumor cells and very little penetrate the cell membrane to enter the tumor cells (50). More recently, a cationic polylysine dendrimer have been shown to have intrinsic antiangiogenic activity in vitro and in vivo assays (51). Intravenous administration of polylysine dendrimer resulted in persistently accumulation in tumor sites, reduction in vascularization, extensive apoptosis/necrosis within the tumor tissue, without any remarkable histological or physiological abnormality in non-tumor tissues such as liver and kidneys (51). Later on, a complexation of doxorubicin (DOX) with cationic poly-L-lysine dendrimer have been developed and shown significant increase in DOX penetration and the toxicity of the drug upon complexation both in multicellular tumor spheroids (MTS), and in vivo solid tumors (52). These evidences clearly show the cationic polylysine and some theirs derivative/drug complexes are capable of bonding and producing a selective toxicity to some tumor cells and tissue mainly due to the electrostatic interaction. Such results give the potential of cationic polylysine dendrimer-drug complexes as synergistic antiangiogenic/anticancer therapeutics to be translated clinically.

Cationic Liposomes

Cationic liposomes, first described in the laboratory of Alec Bangham for the purpose of studying membrane diffusion (53), have been used for a variety of delivery systems for cancer and other disorders (54). In comparison to other gene delivery modes, such as viral vectors, cationic liposomes have significant advantages in terms of simple to synthesis, more biologically safety, and the ability of tailoring for specific applications (55).

Tumor angiogenesis is a formation of neovessels from preexisting vessels in solid tumors, which is a consistent feature of tumors and critical for the support of tumor growth and progression, not only by providing nutrients, oxygen, growth factors and other substances to tumor cells, but also by allowing metastatic cells into circulation (56). It has been proven that the angiogenic tumor vasculature also carries large more amounts of negative charge than peripheral normal tissue (57). Many studies have been developed to investigate the quite selective targeting of cationic liposomes as carrier system for delivering anticancer agents to angiogenic tumor vasculature and tumor cells. It has been shown by Thurston et al. (58) that angiogenic blood vessels in tumors bound and took up cationic liposomes much more than the corresponding normal vessels. Confocal microscopic measurements showed that angiogenic endothelial cells in tumors more bound and uptake fluorescently labeled cationic liposomes with average 15-33 times than corresponding normal endothelial cells. Angiogenic endothelial cells in the model of angiogenesis also selectively took up DNA at cationic liposome complexes, but not anionic, neutral, or sterically stabilized neutral liposomes (58). Further research by Krasnici et al. (57) demonstrated that cationic liposomes but not anionic or neutral liposomes preferentially accumulated in the A-Mel-3 melanoma tissue and tumor vasculature of hamster up to 3-fold compare with normal surrounding host tissue when administered intravenously. The preferential uptake of cationic liposomes in the solid tumor was mainly caused by a highly selective accumulation of liposomes within angiogenic tumor microvessels, whereas neutral and anionic liposomes extravasated unspecifically into the parenchyma several minutes after intravenous injection. Similarly, Nomura et al. (59) reported that clearance of positively charged liposomes was greatly retarded in contrast to neutral liposomes, which immediately appeared in the venous outflow perfusate following intratumoral injection. The preferential and prolonged accumulation in angiogenic tumor vessels seems to be a general feature of cationic liposomes, independent of a certain tumor type. Campbell et al. compared the biodistribution of negatively charged liposomes (−20 mV) and positively charged liposomes (+31 mV) after intravenous injection into tumor-bearing mice (60). While liver was the major destination for both formulations, positively charged liposomes showed higher association with tumor blood vessels than negatively charged ones. Further investigation showed that an increase in cationic lipid from 10 to 50 mol% in PEG-coated cationic liposomes led to a 2-fold increase in liposomal accumulation in tumor vessels, suggesting cationic charge determine the distribution of liposomes between the vascular and extravascular compartments of tissue (60). Recently, using a tumor-bearing mouse model, Abu Lila et al. (61) emphasized that PEG-coated cationic liposomes showed 2-3-fold higher accumulation in tumor tissue than PEG-coated neutral liposomes. This enhanced intra-tumor accumulation was ascribed to the selective binding of PEG-coated cationic liposomes, not only to tumor angiogenic vessels, but to tumor cells as well. Schmitt-Sody et al. (62) demonstrate that cationic liposomes maintain their ability to selectively accumulate tumor vasculature and tumor tissue as compared with surrounding normal tissue after encapsulation of the cytotoxic drug paclitaxel. Moreover, the tumor growth revealed a remarkable retardation after treatment with paclitaxel encapsulated in cationic liposomes in comparison with any other groups, which demonstrated that treatment

with this liposomal formulation significantly increased the antitumor efficacy of the cytotoxic drug paclitaxel. Similarly, Kunstfeld et al. (63) also demonstrated that paclitaxel encapsulated in cationic liposomes diminishes tumor angiogenesis and inhibits melanoma growth in SCID mice. In contrast, paclitaxel administered in its normal Cremophor EL medium, while showing an inhibitory effect in cell culture, was unable to significantly decrease angiogenesis and tumour growth in vivo.

As described above, the promising characteristics of cationic liposomes as carrier system for the delivery of anticancer agents to tumor cells and tumor microenvironment are strongly takes advantage of the natural affinity of cationic surface of those carrier systems for anionic sites in the tumor microvasculature and the surface of tumor cells. Many liposomal drugs have approved for cancer therapy notably Doxil for doxorubicin (Johnson & Johnson, New Brunswick, USA), Lipusu for paclitaxel (Luye Pharma Group, Yantai, China), and Marqibo for vincristine (Talon Therapeutics, South San Francisco, USA) (64, 65). Cationic liposomes have been showing promising development prospects in oncology clinical pharmacology and therapeutics.

Host Defense Peptides

Natural antimicrobial peptides (AMPs), also referred to host defense peptides (HDPs) as a more generic term, constitute a major component of the ancient, nonspecific innate defense system in a variety of multicellular organisms. They were initially discovered because of their antimicrobial activity (66, 67). Despite the diversity in their amino acid sequences and secondary structures, HDPs share many common features, including amphipathic, small size (generally 12-50 amino acids), have an overall net positive charge and have a high content of cationic and hydrophobic residues (67, 68). HDPs have a very high affinity with negatively charged microorganism membranes. They also have a strong tendency to form polymers with a staved-barrel shape. The positively charged portions face the center and form a water channel. The hydrophobic portions fuse with the lipid bilayers. Thus the cationic peptides form water-permeable pore on the plasma membrane of target cells (67). Interestingly, a large number of HDPs not only have the ability to kill both Gram-positive and Gram-negative bacteria, but also exhibit a broad spectrum of cytotoxic activity against cancer cells (67). Some of these peptides have been found to have lipopolysaccharide (LPS) neutralizing ability and the capacity to recruit the adaptive immune response (69). While not all HDPs are able to kill cancer cells, recently, the antimicrobial peptide database lists more than 100 natural host defense peptides with antitumor activity (70). Unlike conventional chemotherapeutic agents which exert a systemic effect and typically target the rapidly dividing cancer cells is often associated with toxicity side-effects caused by inadvertent drug-induced damage to healthy cells and tissues, most of these cationic HDPs have been found to target the membrane of cancer cells, leading to cell lysis and death, which followed the similar mechanism of anti-bacteria. Thus, HDPs offer the possibility of a new family of therapeutic agents, which are different with or complementary to existing chemotherapeutic agents and have shown the ability to bypass the multidrug-resistance mechanism (71). Due to the altered metabolic abnormalities of malignant cells, fundamental differences exist between the cell membranes of malignant cells and normal cells. These differences likely account for the ability of certain HDPs to kill cancer cells specificity while have less effect of healthy cells. In this regard, electrostatic interactions between cationic HDPs and anionic cell membrane components are believed to be a major factor in the selective killing of cancer cells by HDPs.

Magainins 1 and magainins 2, originally isolated from African clawed frog Xenopus laevis skin, exhibited in vitro the antibiotic activity on both Gram-positive and Gram-negative strains of bacteria, fungi, and protozoa (72, 73). It was suggested that these peptides act on the phospholipid of the plasma membrane to perform antimicrobial activity (74). In 1990, Cruciani et al. (75) reported that magainins and synthetic analogues can rapidly and specifically lyse hematopoietic tumor and solid tumor cells with a relative cytotoxic potency that parallels their antibacterial efficiency and at concentrations that are relatively nontoxic to well-differentiated cells. Magainin G showed the most selectivity cytotoxic for tumor cells, which have virtually no cytolytic effect on peripheral blood lymphocytes (PBLs) and polymorphonuclear neutrophils (PMNs) after 60 min of incubation at a concentration twice of that required to lyse 100% of tumor cells in 10 min (75). Ohsaki et al. (76) have investigated the antitumor activity of Synthetic magainin A and magainin G against six small cell lung cancer (SCLC) cell lines. The results suggested that magainin A and magainin G showed consistent growth inhibition against all six SCLC cell lines. Meanwhile, these peptides were less effective against normal human fibroblast cells than malignant cells. In vivo efficiency research against murine ascites tumors has shown that Magainin 2 and two more analogues had activity against P388 leukemia, S180 ascites, and a spontaneous ovarian tumor by increasing in life span of over 100% when injected i.p.. The antitumor activity was suggested to be related to short duration non-receptor-driven contact with target cell membranes (77). Papo et al. (78) have reported that a new series of cationic diastereomeric peptides are highly toxic and selective toward cancer cells compared to normal cells. It was suggested that the cell selectivity was predominantly determined by improved electrostatic attraction of the peptides to an increase in the level of large amount of acidic components on the surface of cancer cells, but may

not by the slight increase in the level of PS in the outer surface of the cancer cell membranes (78). Another similar peptide, a 15-amino acids diastereomer composed of D - and L - leucines, arginines, and lysines, was shown to act against the mouse melanoma and lung carcinoma cell lines and to significantly inhibit lung metastasis in mice with no detectable side effects (79). An intratumorally injection of a 15-mer all L-amino acids lytic peptide and its diastereomer completely inhibited the growth of both androgen-dependent and androgen-independent human prostate carcinomas without affecting the nonmalignant neighboring cells (80). A necrotic mechanism of killing rather than an apoptotic was suggested, which involves four major steps in the following process: (a) amphipathic-D binds initially to distinct sites on the negatively charged cytoplasmic membrane, which is governed mainly by electrostatic interactions, and then it reaches a threshold concentration; (b) Membrane binding forces the peptide to adopt a functional structure, which allows the peptide induces marked membrane depolarization; (c) the kinetics of membrane permeation is fast followed by an equal distribution of the peptide in the cytoplasm; and (d) the cells become necrotic (80). This electrostatic interaction induced cancer necrocytosis model was recognized as the typical cancer killing mechanism of cationic HDPs (71, 81, 82). Certainly, besides of the electrostatic interaction of HDPs with the surface of cancer cells, a great deal of further study must be devoted to studying the structure, dynamics, topology of the activated HDPs and which of the characteristics of a cancer cell make some HDPs preferentially target them.

Moreover, in human body, non-immune cells usually synthesize cationic peptides at low levels. Therefore their defensive abilities are much lower than that of innate immune system. In contrast, granulocytes can produce cationic human neutrophil peptides (HNPs) at extremely high level of 10 mg/ml. This ability would make granulocytes the most effective immune cells to kill cells with negative charges on their surfaces. Recently, Z. Cui et al. reported a serendipitous discovery of a cancer complete resistant/ spontaneous regression (CR/SR) "super-mice" family (83), in which it showed that the cancer resistance in SR/CR mice was mediated by the special immune system, exactly the innate immune system with neutrophils act as the main effective attacking cells (84, 85). In a similar way as the antimicrobial action of HDPs, the cancer killing process of neutrophils from SR/CR mice were investigated and showed by three phases: infiltration, tight contact and tumor destruction (85, 86). Although the exactly mechanism at gene level of this unique recognition reaction have not been clarified, the cationic peptides releasing from neutrophils and the unique surface negative charge property of cancer cells are considered as the main factors of cancer cell targeting and destruction mechanisms (87, 88).

DEAE-Dextran

Diethylaminoethyl-Dextran (DEAE-Dextran), as a polycatonic derivative of Dextran, has been used in many applications in molecular biology and the health-care sector, such as in DNA transfection (89), gene therapy (90), and enhancer of viral infectivity (91). The effect of different DEAE-dextran derivatives varied in molecular weight and charge density (degree of substitution with diethyl-amino-ethyl groups) on the surface charge of tumor cells has been investigated by Thorling et al. (92) It was shown that the higher molecular weight and higher degree of substitution gave a stronger binding to the tumor cell surface and the ability to neutralize the negative charge of the cell surface (92). In addition, it has been shown in the *in vivo* experiment results that the most effective inhibitory effect on the growth of transplanted tumor was obtained by the highest degree of positive charge density in DEAE dextran, which seems that the effect of the compounds on the negative electric charge of tumor cell surface is essential for the inhibitory effect observed in these experiments. It is worthwhile to note that cells previously treated with neuraminidase and subsequently incubated with labeled DEAE dextran would also bind the DEAE dextran. It is supposed in these instances that the DEAE dextran is bound to other acid groups on the cell surface which have been exposed after removal of the sialic acid component of the mucoprotein layer (92).

Summary

Bioelectricity is the sign of life. Cellular electricity is present in every life form and in every living cell. It plays essential roles in intercellular and intracellular communication, energy production and many designated cellular functions. Cancer cells are a class of pathological cells with profoundly altered energy metabolism and cross-membrane flow of ions. From 1940s, the phenomenon that cancer cells gain abnormal surface electrical charges has been discovered and investigated via different tools, such as micromanipulator, microscopy, cell electrophoresis, polyelectrolyte and positively charged nanomaterials assisted pathomorphology studies. Due to the lack of an effective tool for the real-time measurement of electrical properties of individual live intact cells, it still has not been understood well about the cancer cellular electricity mechanisms. In other words, the unique surface charge property of cancer cells and the interchange of cellular electricity does not seem to get enough attendance although enormous efforts has been paid for cancer research as a general research field. In this article, we give a historic perspective review about the discovering, investigating and application of the abnormal surface electrical properties of cancer cells. Although it is still difficult to fully understand the unique properties of cancer cells. We reasonably propose that the significantly enhanced surface negative charge of cancer cells may be a neglected hall-

mark of cancer which cannot be overstated. Perhaps, with the onset of innovative technologies, the surface electrical properties of cancer cells can attract sufficient efforts to further understand their mechanisms and implications in the therapeutic and diagnostic purposes of cancer.■

Conflict of Interests

None

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