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Mini Review

Dielectric Properties of Red Blood Cells for Cancer Diagnostics and Treatment

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Abstract

Imaginary parts of complex dielectric permittivity of the aqueous suspensions of the RBC and RBC ghosts of 28 healthy donors (control group) and 62 patients with breast and lung cancer have been measured in the broad temperature range (1÷46°C) by the electrometer of resonant type at the operating frequency f=9,2 GHz that correspond to the resonance of water molecules. The differences in the dielectric parameters of the healthy and cancer blood have been detected. The dielectric permittivity increases in the cancer blood independently on the cancer type in both RBC and ghosts' suspensions. The phase angle of the complex permittivity is always higher in healthy donors, while in the ghost's suspensions the difference is not such pronounced. The temperature dependencies of the dielectric parameters determined by the structural changes of the RBC membranes, conformational changes of the membrane channels, ion leakage, changes in the protein spectrum and membrane fluidity, membrane loosening and the hydrated shell thickness are presented. In that way, the dielectric parameters perfectly reflect the functional state of the RBC membranes affected by cancer and are very important for early diagnostics of cancer as well as for monitoring the success of the treatment.

Keywords: Cells; Dielectric Permittivity; Cancer; Microwave Spectroscopy; Medical Diagnostics

Abbreviations

EMF: Electromagnetic Field; MW: Microwave; RBC: Red Blood Cells

Introduction

Cancer morbidity permanently grows all over the world, and according to the International Agency for Research on Cancer (IARC), there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide, where 90% of them are caused by metastasis [1,2]. Recently the World Health Organization (WHO) has reported statistical evidence on the global epidemiology of cancer [3]. Until now > 200 types of cancers have been discovered [4], and early cancer diagnosis is essential for positive prognosis of cancer treatment and active life prolongation [3]. Different hereditary factors and external mutagenic influences promoted development of pathologic changes of metabolic processes starting from the cellular level. As it was stated by World Cancer Research Fund, over 20-32% of cancer deaths could be avoided by reducing overweight, ceasing alcohol uptake and cigarette smoke, enhancing physical activity, and improving the nutrition [5]. A series of biochemical studies like prostate specific antigen screening for prostatic cancer, fecal occult blood test for colorectal cancer, as well as traditional biomarkers are used for cancer diagnostics [6].

Since red blood cells (RBC) continuously circulate in the blood circulation systems and are influenced by the specific antigens, products of the tissue decay and other factors, their properties are significantly influenced by the disease development and, therefore, can be used for early diagnostics of cancer or/and for control over the treatment efficiency based on the tendency of restoration of the RBC properties towards the correspondent healthy values [7]. The blood samples can be easily getting from the vein, and mechanical (deformability), dielectric (permittivity), optic (light scatter), magnetic (diamagnetic or paramagnetic) and some other physical properties and their temperature dependencies can be easily estimated by laboratory equipment [8].

The RBC membranes being in close interaction with cells and tissues of the body are influenced by the cell metabolism, tissue microcirculation and external physical factors as X- ray, chemotherapy and others [9].

The reaction of the RBC on the malignant tumor growth is similar to their changes at inflammatory pro-cesses of different nature and location and influence of the toxic chemical substances [10]. In spite of the great number of studies dedicated to the RBC parameters in the native suspensions and aqueous solutions, many essential features of their properties remain understudied especially for the patient-specific scenario of the disease development and treatment [11-13]. The changes in functional state of RBC in cancer patients correspond to the changes in the hydration shells of their membranes [14]. The thickness and structure of the hydration shells can be studied by the MW dielectrometry, for the water molecules are influenced by the electromagnetic fields (EMF) in the MW frequencies [15,16]. Before dielectric properties of native blood, and aqueous suspensions of RBC and their ghosts have been studied in the broadband EMF [17-20]. The MW EMF studies of the blood and blood cells are rare [21-23]. The changes in the MW dielectric properties of RBC in patients with cancer [24-26] and stroke [27,28] have been studied, the protective anticancer action of Nano diamonds has been observed [29], and the nanolayered theoretical model for calculation of the RBC's electrophysical properties has been developed [30,31]. In this paper the dielectric indexes of RBC for the cancer diagnostics and treatment efficiency estimation are studied.

Material and Methods

The venous blood samples have been taken from the control group of 28 healthy donors, and 62 patients with breast and lung cancer (I-III stages by TNM classification); the average age was 47 ± 4 years. The blood samples with sodium citrate (0.11 M) was centrifuged (3000 min^{-1}), and plasma with leukocytes have been removed. The remained RBC suspension was washed three times with saline (0.15 M NaCl, 10 mM Na-phosphate buffer of pH 7.4) and centrifuged during 10 min. The RBC sediment was then resuspended in an isotonic solution 0.15 M NaCl at a constant RBC concentration 4.5–5 x 103 cell/mm^3. For the second set of experimental measurements the RBC ghosts have been obtained by osmotic haemolysis followed by washing in the centrifuge and then resuspended in sodium chloride. The aqueous suspensions of RBC ghosts with the same concentrations have been prepared.

The MW di electrometer of resonant type at the operating frequency of f = 9,2 Ghz [32,33] has been used for the direct measurements of the real ε' and imaginary ε'' parts of complex dielectric permittivity of the RBC suspensions and their ghosts relative to pure water in a wide range of the ambient temperatures . The complex dielectric permittivity can be written in a standard trigonometric form as $\varepsilon^* = \varepsilon' + \varepsilon'' = \varepsilon \cdot exp(i\,\theta)$, where $\varepsilon = \sqrt{(\varepsilon')^2 + (\varepsilon'')^2}$ $\theta = arctan(\varepsilon''/\varepsilon')$, where θ is the phase shift between the external EMF and the polarization field in the suspension and it is determined the dielectric loss in the medium. The phase shift depends on the confinement of the molecules participated in the polarization processes. At the studied frequencies f=9,2 GHz those are mostly water molecules and the dielectric loss is mostly determined by the ration between the free bulk water and the confined molecules in the hydrate shells [14,17,21]. The methods of variation statistics have been applied to the measurement and computational data.

Results and Discussion

The results of the measured values $\varepsilon'(T)$ and $\varepsilon''(T)$ for the RBC suspensions of healthy donors, patients with breast cancer and lung cancer are presented in figure 1 a,b. As it is shown in figure 1a, the dielectric permittivity increases in the case of the cancer blood independently on the cancer type. As it was discussed in [25,26], the increase in the dielectric permittivity is connected with a decrease in the thickness of the hydrated shells of the affected RBC and the structure of the water shells composed by the water molecules bond to the membrane. As in the aqueous solutions the dispersion in the microwave range corresponds to the behaviour of water molecules in the EMF [12,16,17,21], it means the hydrated shells become lees compact and organized due to the changed membrane properties. It worse noting, the dielectric permittivity ε' in this case is a non-specified index of cancer. Since similar changes in ε' have also been revealed for the blood of the patients with ischemic and hemorrhagic stroke [27,28], one may conclude the dielectric permittivity perfectly reflects the functional state of the RBC membranes affected by severe diseases of different nature. The corresponding changes in ε'' are not that obvious (figure 1b). Note, the dielectric permittivity ε' has clear physical meaning and characterizes a polarization ability of atoms and molecules, while the value ε'' has no clear physical meaning and only its combinations with ε' and some other electric parameters reflects the biophysical variations of the complex structures in aqueous solutions.

As it has been discussed in [26], in the temperature range T= 6-12^{0}C, 17-40^{0}C, 43-46^{0}C in the RBC and RBC ghost suspensions of healthy individuals the breaks attended with an increase of AE in 18,4 kJ/M at 12^{0}C, a decrease in 4,6 kJ/M at 37^{0}C, and growth of AE at 43-46^{0}C with 17,31 kJ/M have been observed. For the cancer blood the changes in the AE have been observed at T = 9-18^{0}C, 43-46^{0}C (breast cancer) and 23-37^{0}C (lung cancer) that is connected with the change of DRF of H_2O molecules. For RBC of the patients with breast cancer an increase of AE in 9,8 kJ/M at T = 9-18^{0}C and in 14,7 kJ/M at T = 43-46^{0}C have been detected. For patients with lung cancer an increase of AE in 8,3 kJ/M at T=23–27^{0}C has been experimentally found.

The same dependencies ε′(T) and ε′′(T) for the RBC ghosts are given in figure 2. Similar regularities in the dielectric constants for the healthy donors and cancer patients have been obtained. In this case the changes are caused by the bilayer membranes of the RBC only. The differences between the healthy and affected RBC membranes are temperature dependent, like it was described in other experiments [25,26]. At the lower temperatures the changes between the healthy and cancer blood are different (figure 2a), but at the body temperatures they correspond to the behaviour of the native RBC (figure 1a) and the cancer of different types produced increase in the dielectric permittivity ε′. The same regularities for the ε′′(T) depend on the cancer type (figure 2b).

Figure 1: Experimental dependencies ε′(T) and ε′′(T) for the RBC suspensions of healthy donors (■), patients with breast cancer (▲) and lung cancer (●).

Figure 2: Experimental dependencies ε′(T) and ε′′(T) for the RBC suspensions of healthy donors (■), patients with breast cancer (▲) and lung cancer (●).

Since cancer occurs a significant influence on the organism, including the RBC membranes, because the specific cancer factors and products of the tissue necrosis influence the RBC membranes [34], the experiments on the RBC ghosts revealed the influence and damage of the cancer directly on the RBC membranes at the body temperatures.

The phase angle values computed from the measured ε′(T) and ε′′(T) data are presented in figure 3. The phase angle in healthy donors is always higher than the ones in the breast and lung cancer patients (figure 3a), while in the RBC ghosts' suspensions the difference is not such pronounced and exhibits dependence on the type of cancer (figure 3b). The bigger angles correspond to the longer times needed for the structured structures like agglomerates of water molecules and hydrated shells to follow the changes in the EMF.

Figure 3: The computed phase shift angle for the RBC suspensions of healthy donors (■), patients with breast cancer (▲) and lung cancer (●).

In that way, it is shown the changes if the dielectric permittivity and dielectric loss of the suspensions of RBC and RBC ghosts are determined by a cascade of changes in the protein spectrum in the RBC membranes, thinning of their hydrated shells, loosening of the membrane surface, increase in the membrane fluidity produced by changes in the membrane transport and leakage of ions [35]. This effect intensifies at lowering of the temperature of medium that is probably connected with the local temperature depending transitions of the lipid components of membranes.

Conclusion

Based on the di electrometry measurement data on the temperature dependencies of real ε′(T) and imaginary ε′′(T) parts of complex dielectric permittivity of the aqueous suspensions of the RBC and RBC ghosts from the blood samples of healthy donors and patients with breast and lung cancer in the broad temperature range (1÷ 46°C), the differences in the dielectric parameters of the healthy and cancer blood have been detected.

It was found, the dielectric permittivity ε′ increases in the case of the cancer blood independently on the cancer type that may be connected with decreasing the thickness of the hydrated shells of the affected RBC and the structure of their hydrated shells composed by the water molecules bound by the membrane [25,26]. Similar changes in ε′ have been revealed in [27,28] for the ischemic blood samples. Therefore, one can conclude the dielectric permittivity perfectly reflects the functional state of the RBC membranes affected by severe diseases of different nature.

The changes in ε′′ caused by cancer are not such clear, the more so as the value ε′′ has no evident physical meaning. The more reliable physical parameter is the phase angle of the complex dielectric permittivity. It was found, the phase angle in healthy donors is always higher than for the samples with breast and lung cancer, while in the RBC ghosts suspensions the difference is not such pronounced and exhibits dependence on the type of cancer. The bigger the angles the longer the times needed for the structured structures like bound water molecules to follow the changes in the EMF.

The temperature dependencies ε′(T) and ε′′(T) are determined by the structural changes of the RBC membranes with temperature including the conformational changes of the membrane channels, ion leakage, changes in the protein spectrum and membrane fluidity, membrane loosening and the hydrated shell thickness.

In that way, both real and imaginary parts of complex dielectric permittivity reflect non-specific pathological changes in the function of the affected RBC and can be used for detailed early diagnostics of diseases like cancer, and also for monitoring of success of the X-ray or chemotherapy.

Conflict of Interest

The authors declare any neither financial interest or conflict of interests.

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