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REVIEW PAPER

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Glycosaminoglycan concentration in cancer tissue

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ABSTRACT

Introduction. Glycosaminoglycans (GAGs) play a widespread role in tissue modelling. GAG polymers may affect several receptor pathways in parallel.

Aim. To present difference in concentration of GAG in healthy and cancer tissues.

Material and methods. The literature search was performed nd reviewed using selected keywords.

Results. We revieved the methods of detection various types of glycans measured by Magnetic Resonance Imaging.

Conclusion. MRI methodology provides an efficient tool forstudy of cellular composition. The use T_1 aof T_2 measurements to study cancer tissue is a promising assay.

Keywords. fixed charge density, glycosaminoglycan, magnetic resonance imaging

Introduction

Proteoglycans (PG) are one of the major components of the extracellular matrix (ECM). ECM conteinat at least one glycosaminoglycan (GAG) chain such as heparan sulfate, chondroitin sulfate, keratan sulfate, and heparin. PGs are formed of GAGs covalently attached to the core proteins. PG are cellular, subcellular, intracellular, cell surface, pericellular, and extracellular.[1-2] PG are major components of extracellular matrix playing key roles in its structural organization and cell signaling contributing to the control of numerous normal and pathological processes.[3-9] GAG expression occurs in most hematological malignancies, notably acute myeloid leukemia, myeloproliferative neoplasms, and multiple myeloma. Here, we review recent research advances regarding cellular GAG and possible magnetic resonance applications to measure GAG concentrations.

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Magnetic Resonance Imaging and celluar GAG measurements

Relaxation times measuremens (T_1 and T_2) of cancer tissue protons can be determined by Magnetic Resonance Imaging (MRI). Because of the development of MRI methods many cellular properties of tumor tissue is studied with MRI. MRI relaxation times have been shown to be various for many types of tumors compared to normal tissues. MRI is an important non-surgical tool in medical and biomedical analysis. While standard MRI can provide basic information regarding tumor location, its size and spread, the quantified MRI can evaluate the effectiveness of therapy. It was already shown that treatment of cells results in MR contrast changes due to changes in relaxivity caused by cell shrinkage and cellular membrane blabbing. We contribute changes in T_1 and T_2 during the cell growth observed for both cell lines to the changes in tissue hydratation and protein content. In addition, our study showed that proton T_1 and T_2 relaxation times are not significantly different between both cell lines.

Glycosaminoglycan (GAG) [9-24]

The GAG concentration was calculated based on Fixed Charge Density (FCD) value, which was measured by flushing the culture with $Gd(DTPA)^{2-}$. The FCD can be expressed as:

$$FCD_{tissue} = -2\left[Na^+\right]_{bath}\left(\sqrt{\frac{\left[Gd(DTPA)^{2-}\right]_{tissue}}{\left[Gd(DTPA)^{2-}\right]_{bath}}} - \sqrt{\frac{\left[Gd(DTPA)^{2-}\right]_{bath}}{\left[Gd(DTPA)^{2-}\right]_{tissue}}}\right)$$

{Eq. 1}

Where:

$$\left[Gd(GDPA)^{2-}\right]_{tissue} = \frac{1}{R}\left(\frac{1}{(postGd)T_{1(tissue)}} - \frac{1}{(preGd)T_{1(tissue)}}\right)$$

{Eq. 1a}

and

$$\left[Gd(DTPA)^{2-}\right]_{bath} = \frac{1}{R}\left(\frac{1}{(postGd)T_{1(bath)}} - \frac{1}{(preGd)T_{1(bath)}}\right)$$

{Eq. 1b}

Where:

Bath – medium around the breast cancer cells;

R – relaxivity (mmol/L/sec);

Tissue – breast cancer cells tissue;

$[Na^+]_{bath}$ – concentration of Na^+ ions in bath, 154 (mmol/L);

$(postGd)T_{1(tissue)}$ – T_1 relaxation time of the breast cancer cells after administration $Gd(DTPA)^{2-}$ solution in sec;

$T_{1(tissue)}$ – T_1 relaxation time of the breast cancer cells before administration $Gd(DTPA)^{2-}$ solution in sec;

$(postGd)T_{1(bath)}$ – T_1 relaxation time of the bath after administration $Gd(DTPA)^{2-}$ solution in sec;

$T_{1(bath)}$ – T_1 relaxation time of bath before administration $Gd(DTPA)^{2-}$ solution in sec.

The calculated FCD is converted to GAG concentration according equation 2:

$$GAG = FCD\left(\frac{502.5}{-2}\right)$$ *{Eq. 2}*

Where: *GAG*- Glycosoaminoglycan concentration (mg/L);

FCD – Fixed Charge Density (mmol/L);

502.5 – Molecular weight of GAG in (mg/mmol).

Application of enables direct study of cells before and after treatment. The T_1 and T2 relaxation time of cells is sensitive to GAG concentration. Therefore, MRI measurements of cells with the use of anionic paramagnetic contrast agent $Gd(DTPA)^{2-}$ reflect directly to the GAG concentration in tissue and is sensitive to physiologic and pathologic conditions resulting in an approximately linear relation between GAG content and T_1 relaxation time. Since GAGs have negatively charged side chains, the $Gd(DTPA)^{2-}$ distributes in higher concentration into areas with lower GAG concentrations. Therefore, a low T_1 values after contrast agent administration indicates low GAG concentration.

In oncology non-invasive imaging of cells has gained interest for the assessment of tumor response to cancer therapy. Therefore, MRI has become an important diagnostic technique for characterization of cells, such as degeneration. Due to variability in response to therapy, there is a growing interest in monitoring efficacy progress during treatment. There is a rapid increase in the applications of MRI for cellular imaging. Table 1 presents selected types of cellular PG's.

Eponym	Secretory granules	Location
Serglycin[24]	Transmembrane	Cell surface
Syndecan[25,26]	Transmembrane	Cell surface
NG2[27,28]	Transmembrane	Cell surface
Betaglycan[29,30,31]	Transmembrane	Cell surface
Phosphacan[32,33]	Transmembrane	Cell surface
Glypican[34,35]	Glypican	Cell surface
Perlecan[36]	Basement membrane zone	Pericellular
Agrin[37]	Basement membrane zone	Pericellular
Aggrecan[38]	Hyalectan Lectican	Extracellular
Versican [39]	Hyalectan Lectican	Extracellular
Neurocan[40]	Hyalectan Lectican	Extracellular
Brevican[41]	Hyalectan Lectican	Extracellular

Conclusion

MRI methodology provides an efficient tool forstudy of cellular composition.The use T_1 aof T_2 measurements to study cancer tissue is a promising assay.

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