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MOLECULAR IMAGING: FUTURE AVENUES/ FRONTIERS OF DIAGNOSTIC IMAGING

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Abstract:

Introduction: *In this study we will discuss different avenues or frontiers of molecular imaging and its future aspects.*

Different avenues of molecular imaging *:*

1-Nanotechnology: *is study of extremely small things and can be applied across all the other basic sciences ranging from chemistry, biology, physics, materials science, and engineering, to handle the matter on an atomic, molecular, and supramolecular level using the principles of mechano-synthesis.*

2-Aquaporin (AQPs): *are members of superfamily of major intrinsic protein. Exception of aquaporin1 (EgAQP1) rest all aquaporin's shows conserved amphipathic channel and NPA signature motifs, which suggests that EgAQPs acts both as water channels as well as other solutes channel proteins.*

Immunofluorescence: *is the immunoassay technique for light microscopy with a fluorescence microscope that uses a detector antibody or an antigen labeled with florescent dyes to specific biomolecule targets within a cell (epitope)*

Discussion: *The role of molecular imagine in diagnostic ultrasound has given us a new insight in to fetal anomalies. While Fluorescence imaging by furnishing a biocompatible technique using noninvasive red fluorescence imaging. New advances in conventional-CT is High-resolution Nano-CT as a radiological transformation in biomedical basic research. Another important avenue in molecular imaging of bio-sensing and diagnostics is RNA nanotechnology for processing information with molecular precision. Lu, J., et al in their study suggested next-generation intelligent MRI contrast agents by inverse contrast enhancement effect. For the purpose of diagnostic imaging of hepatic lesions magnetic resonance imaging (MRI) contrast agents braced with Iron oxide nanoparticle (IONP) have been widely employed. IVIS and MRI imaging was harnessed in mice by secreting HMGB1 in vitro and in vivo to envisage intracranial tumors. The advent of extraordinary chemical exchange saturation transfer (CEST), has enabled us to paving way for drug delivery systems based on image-guided biopolymers.*

Conclusion: *The application of molecular imaging in the field of diagnostic imaging and clinical diagnostics are unlimited. it is important to assess the sine qua non grounding for crafting a comprehensive yet optimistic methodology for the future aspect. This encourages the future clinical researchers to devise molecular imaging probes of greater clinical significance. The correct integration of diagnostic imaging techniques and molecular approaches to make sure the best diagnostic output.*

Key words: *Molecular, Aquaporin (AQPs), Immunofluorescence, Fluorescent probes, nanotechnology, magnetic resonance imaging (MRI).*

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INTRODUCTION:

Present diagnostic imaging modalities can ascertain different anatomical variants and anomalies but cannot differentiate between diagnostic, prognostic, predictive and therapeutic biomarkers of many disease processes at molecular level, giving many false positive and false negative results like infections of specific pathogens, or delineate the extent of an infection, and differentiating many disease process from diagnosing to treatment to cure. Molecular imaging is the answer to those uncertainties using aquaporin, Immunofluorescence imaging, in vivo fluorescence, bioluminescence imaging, RNA nanotechnology coupled with electrochemical bio-sensing for real time imaging of biomolecules, achieving diversity in structure and function in living cells.

Different avenues of molecular imaging:

2.1-Aquaporin's

Peter Agre said Aquaporin's are "the plumbing system for cells,". The discovery of the aquaporin water channels mechanism by which water passes through biological membranes is a great breakthrough in scientific research. Efficient regulation of water homeostasis is essential component of all living cells as aquaporin proteins are found in all organisms from micro to macro levels. The structure of aquaporin's is subjected to billions of years of evolution. The designated AQPs was named after the major intrinsic protein (MIP) of mammalian lens fibers. [1,2] AQPs represents all kingdoms, from archaea to mammals (number of aquaporin's found in mammals are thirteen) [3,4]. At amino-acid level the structure similarity to human channel proteins is bacterial aqua-glyceroporin GlpF with sequence similarity less than 30%. [5]

2.2-First Aquaporin discovered

The first aquaporin to be discovered and extensively studied was human erythrocyte membrane reported by Peter_Agre, of Johns Hopkins University. 'aquaporin-1'(AQP1) originally named as CHIP28. [6,7,8]

2.3-Pioneering Discovery of Aquaporins/Award

Peter Agre and his colleagues were awarded with the Nobel Prize for Chemistry in 2003 for describing the first aquaporin. [6,7]

2.4-Structure of Aquaporin's

Aquaporin's are six transmembrane helices membrane proteins (all aquaporin's are structurally related) from a larger family of major intrinsic proteins (MIP). The membrane protein is connected by five loops, three loops are extracellular and two loops are intracellular, with two internal tandem repeats of protein at amino- and carboxy-terminal halves. Aquaporin's are arranged in a right-handed bundle, with the amino and the carboxyl termini located on the cytoplasmic surface of the membrane, which selectively allow water or other small uncharged molecules to pass along the osmotic gradient as pore forming integral membrane proteins. [9,10,11,12]. Each tandem repeat comprises of three transmembrane helices and a highly conserved loop followed by second transmembrane helix with each loop containing an NPA (asparagineproline-alanine) conserved signature motif. α-helix and random coil were the main secondary structures of echinococcus aquaporin's that fold back into the membrane from opposite sides, with each loop entering membrane through cytoplasmic side and extracellular side respectively. Three to six transmembrane regions with aquaporin's, which indicated multiple hydrophobic regions. An aqueous pathway through the proteinaceous pore is formed in which two NPA boxes are aligned to each other at 180 degrees in a transmembrane domain. [10,12]

2.5-Aquaporin's channels

AQPs are members of superfamily of major intrinsic protein. Exception of aquaporin1 (AQP1) rest all aquaporin's shows conserved amphipathic channel and NPA signature motifs, which suggests that AQPs acts both as water channels as well as other solutes channel proteins. [12]

2.6-Types of Aquaporin's

Aquaporins were divided into three branches, strict aquaporins, aqua-glyceroporins and super-aquaporins (S-aquaporins) .First group also known as water channels, selectively conducts water and the second group conducts small uncharged solutes (volatile substances) , such as glycerol, CO_2, ammonia and urea across the membranes and the third group called the super-aquaporins with unusual NPA boxes, subcellular aquaporins. [13] However charged particles such as protons are completely impermeable through water channels pores, that conserves electrochemical potential difference of membranes. [11,14]

Conclusive studies suggest, we have yet to understand a lot about the aquaporins. Further detail work on understanding the structure and function is needed. The role of aquaporins in medicine, early diagnostics procedures and molecular imaging is making it the potential study of future, with properly manipulated, that could potentially solve medical problems such as fluid retention in heart disease, brain edema after stroke, kidney function, loss of vision, starvation and parasitic diseases. [15] [16,17] some studies also

suggested that angiogenesis, wound healing, organ regeneration and carcinogenesis is also related to AQP1. [18].

3-Immunofluorescence

According to Lim et al., 2005, Immunofluorescence is the immunoassay technique for light microscopy with a fluorescence microscope that uses a detector antibody or an antigen labeled with florescent dyes to specific biomolecule targets within a cell (epitope), labeled either by direct fluorescent antibody (Primary immunofluorescence) method, or the indirect fluorescent antibody (Secondary immunofluorescence) method.

3.1-Fluorescent probes are widely utilized for noninvasive fluorescence imaging. Continuing efforts have been made in developing novel **fluorescent probes** with improved fluorescence quantum yield, enhanced target specificity, and lower cytotoxicity. Before such probes are administrated into a living system, it is essential to evaluate the subcellular uptake, targeting specificity, and cytotoxicity in vitro. Before a fluorescent probe is administered in to living animals for in vivo imaging, it is critical to investigate the biological characteristics of the probe in cells to answer the following questions. How much cellular uptake of the probe may be achieved in target cells? What is the binding affinity between the probe and the target receptor or cellular function (pH, oxygen level, ions etc)? Is the probe safe for cellular and animal studies? An ideal fluorescent probe should have good cellular uptake, strong and specific binding affinity towards the target, and low toxicity.

3.2-Protocols

This collection of protocols provides a basic guide for the evaluation of fluorescent probes by addressing each of these essential questions, and includes the following sections: (1) evaluation of cellular uptake and localization using fluorescence microscopy, (2) evaluation of binding specificity using multiplate reader, and (3) evaluation of safety profile using cytotoxicity assay.

3.3-Staining agents

It is critical to choose a staining agent with distinct spectroscopic region from that of the in vivo fluorescent probe to avoid signal mixing. Some of staining agents prefer living cells; some others can only be used in fixed cells; whereas the rest may work in both conditions. Many agents have been developed to indicate specific cellular structures, such as plasma membrane, cytoskeleton, cytosol, endoplasmic reticulum, endosomes, Golgi complex, mitochondria, nucleus, lysosomes, and peroxisome. Advanced fluorescent staining agents can also act as sensors to provide physiological information such as pH value[19], intracellular oxygen level [20], or reactive oxygen species (ROS) production level [21]. Some can even be activated and switched on/off upon binding with specific target or cleaved by certain enzymes [22, 23]. As such, fluorescent microscopy has become a powerful tool to evaluate fluorescent probes in vitro.

4-Nanotechnology

Nanotechnology is study of extremely small things and can be applied across all the other basic sciences ranging from chemistry, biology, physics, materials science, and engineering, to handle the matter on an atomic, molecular, and supramolecular level using the principles of mechano-synthesis with at least one dimension producing engineered nano-systems in the field of nanomedicine, organic chemistry, surface science, nanoelectronics ,molecular engineering, molecular biology, semiconductor physics, biomaterials, energy storage, microfabrication, consumer products and macroscale products sized at 1-100nm associated with the molecular assembler, also known as molecular nanotechnology(molecular manufacturing).As defined by size, the scope of this technology refers to all the broad range of research which are below the given size threshold and applications whose common trait is specific size thus also known as nanoscale technologies .

The basic idea of nanotechnology to see and to control individual atoms and molecules was first conceived by Richard Feynman. The term coined in 1974 by Norio Taniguchi as "nano-technology".

This technology has been most frequently applied in our basic health care from hundreds of years and will have more significance in years to come.[24] The progression of nanotechnology as drug delivery vehicles has warranted it as one of the most important podiums in medicine for developing diagnostic and therapeutic radiotracers due to their tumor targeting ability, fabricating a tumor diagnostic probe, theranostic agents and small size (≤100 nm) for both diagnostic and therapeutic applications. [25, 26] This technology is giving new insight in to applications in medicine, nanotechnology and biotechnology. The significance of silver nanomaterials is of great importance in our daily life as biomedical, anti-microbial agents, molecular imaging probe for tumor diagnosis**,[**25] water treatment devises, thermal conductivity, jewelry, photography, catalyst activity, and electronic as well different scientific application.[24]

Nanotechnology provides novel strategies for the treatment and diagnosis of cancer. Advances in metallic nanotechnology have gained interest among researchers due to its exclusive vantage of being faster, safer, biocompatible and economical over other conventional methods.[27]

DISCUSSION:

In this study we briefly discuss different important aspects of molecular imagine and its applications in different filed from ultrasound to CT-scans to MRI.

The role of molecular imagine in diagnostic ultrasound has given us a new insight in to fetal anomalies. Besides, clinical routine prenatal ultrasounds lacking reliable sonographic markers, cannot detect all the disorders resulting from monogenic or microdeletion/microduplication disorders. Disorders detected in ultrasounds such as structural anomalies, gender or fetal size discordance can be misleading. Amalgamation of different imaging and molecular techniques is mandatory to abate considerable diagnostic discrepancies. The increased prevalence of assisted reproductive techniques (ARTs) with increased maternal age is followed by increased demand for prenatal care and diagnostic intervention in order to diagnose and better classify the effected fetuses, if genomic aberration was detected. The correct integration of diagnostic imaging techniques and molecular approaches to make sure the best diagnostic output. [28] Nguyen, Mitchison et al in their studeis have clearly illustrated early developemental process on cellular level of amphibian oocytes and embryos, how the cell division machinery conforms to changes in embryonic cell sizes and use of immunofluorescence for imaging mitotic spindles, microtubule asters, chromosomes, nuclei and microtubule assemblies [29].The following method can be useful for imaging embryonic changes in fetuses in early fetal life.

According to the ACS journal *Nano Letters*, traditional prenatal imaging and other diagnostic tests are unreliable in diagnosing down syndrome with accuracy. Researchers have reported in ACS journal *Nano Letters by using field-effect transistor biosensor chips*, developed a sensitive new biosensor used to detect fetal Down syndrome DNA by detecting DNA concentrations as low as 0.1 fM/L in pregnant women's blood.

Fluorescence imaging by furnishing a biocompatible technique using noninvasive red fluorescence imaging coupled with electrochemical bio-sensing for qualitative and quantitative locus by single labeling platform. Red fluorescence of DNA-AgNCs elucidates the cancer cells and electrochemical signals of DNA-AgNCs accredit improved sensitivity.[30]A fluorescent probe could noninvasively image-guide target oriented implant infections ,diagnosing both acute and subacute implant infection, debridement of infective tissues for better clinical management and post-infectious care.[31]

New advances in conventional-CT is High-resolution Nano-CT as a radiological transformation in biomedical basic research, it is one of the finest high-resolution cross-sectional advancement of micro-CT imaging in consideration of other high resolution cross-sectional imaging techniques. the potential of Nano-CT signifying focal spot image of less than 400nm in diameter. A superior spatial resolution is achieved by incorporating exclusive imaging detectors and protocols. Nano-computed tomography demonstrates high spatial resolution for imaging of imaging of lungs, cerebral micro-circulation.[32]

Another important avenue in molecular imaging of bio-sensing and diagnostics is RNA nanotechnology for processing information with molecular precision by devising advanced biosensors interfacing RNA-based devices with collaborative podiums. The RNA nanotechnology modules and components are genetically engineered for real time imaging of biomolecules, achieving diversity in structure and function in living cells. RNA nanotechnology assembled with bioanalytical chemistry, sensing of target molecules and gene expression can be accomplished by employing interactions of RNA modules [33] .The use of stem cell Nano-composites and allogeneic stem cell transplants for the treatment of degenerative bone diseases as a therapeutic application of this technology.[34]

Lu, J., et al in their study suggested next-generation intelligent MRI contrast agents by inverse contrast enhancement effect, reported by i-motif DNA-assisted pH-responsive iron oxide nanocluster assemblies (termed RIAs) by disassembly of the RIAs in the acidic micro-environment of the tumor, leading to decrease in tumor relaxivity ratio, effectively translating RIAs from a T2 to T1 contrast agent, in order to better classify normal liver and HCC tissues. This inverse contrast enhancement was validated on an orthotopic HCC by hypo-attenuating normal liver versus hyper-attenuating HCC under T1 imaging.[35]

For the purpose of diagnostic imaging of hepatic lesions magnetic resonance imaging (MRI) contrast agents braced with Iron oxide nanoparticle (IONP) have been widely employed. The IONAs in tumors are easily demounted in acidic microenvironment into a

large number of hydrophilic extremely small-sized iron oxide nanoparticles (ESIONs), the hydrazone bonds are cleaved resulting in highly enhanced T1MR contrast is achieved, IONAs was also authenticated in vivo, exhibiting an unprecedented T1MRI imaging methodology for highly sensitive acidic tumors. Confirmed by estimation of r1 values at different pH conditions. [36]

HMGB1 is highly expressive by binding to and activating TLR and RAGE receptors with increased progression and angiogenesis of glioma.[37] It is a prominent DNA-binding nuclear protein in many cancers. [38] Hong, B., et al in there research have described the significane of utilization of HMGB1 in glioma xenografts after viro-therapy, in vitro and in vivo.[39, 40] IVIS and MRI imaging was harnessed in mice by secreting HMGB1 *in vitro* and *in vivo* to envisage intracranial tumors, tumor growth, tumor microenvironment, virus spread, changes in edema and resorted to oncolytic viral therapy by application of HMGB1-blocking antibodies. Resulting in better survival of mice treated with OHSV. [39] Hong, B., et al concluded that proper estimation of HMGB1 could prove to a reliable marker in patients of intercranial neoplasms with life-threatening edema and intracranial inflammation. [39]

Oligodendrogliomas are now classified according to the presence of specific molecular signature (IDH mutation and 1p19q codeletion) by WHO Classification of CNS Tumors of 2016, the following molecular marker easily distinguishes astrocytoma's from oligodendrogliomas.[41]

The advent of extraordinary chemical exchange saturation transfer (CEST), has enabled us to expound hydroxyl protons-rich sugar-based biopolymers as sensitive and translatable molecular imaging MRI agents and paving way for drug delivery systems based on image-guided biopolymers.[42]

CONCLUSION:

The role of molecular imagine in diagnostic ultrasound has given us a new insight in to fetal anomalies. While Fluorescence imaging by furnishing a biocompatible technique using noninvasive red fluorescence imaging coupled with electrochemical bio-sensing for qualitative and quantitative locus by single labeling platform elucidates the cancer cells.

New advances in conventional-CT is High-resolution Nano-CT as a radiological transformation in biomedical basic research, it is one of the finest high-resolution cross-sectional advancement of micro-CT imaging. Another important avenue in molecular imaging of bio-sensing and diagnostics is RNA nanotechnology for processing information with molecular precision by devising advanced biosensors interfacing RNA-based devices with collaborative podiums.

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The application of molecular imaging in the field of diagnostic imaging and clinical diagnostics are unlimited. The avenues of molecular imaging from macro to micro-imaging is the future of all diagnostic in clinical medicine. We need to step-up and have courage to explore all the possibilities in all research fields. This article concludes the importance of molecular imagine and paves a way in rite direction for all researchers and clinician for future course of action. It's the need of the hour to take a leap of faith in rite direction to classify and categorize diseases at molecular level. More resources should be directed in this direction; researchers should be aided by organization at large scale to get the best desired results. it is important to assess the sine qua non grounding for crafting a comprehensive yet optimistic methodology for the future aspect. This encourages the future clinical researchers to devise molecular imaging probes of greater clinical significance.

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