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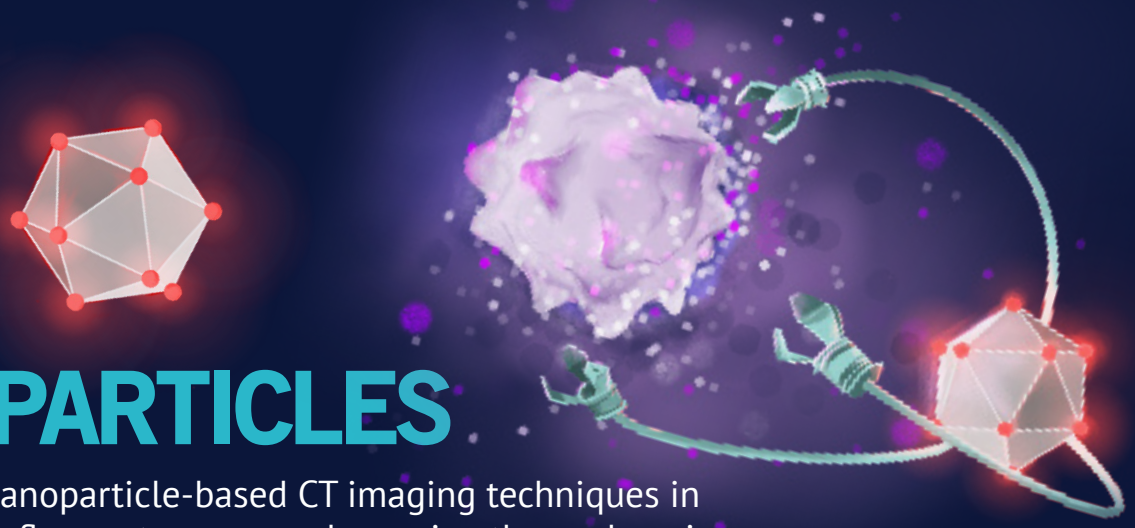

Opinion

NANOPARTICLES

The efficacy of nanoparticle-based CT imaging techniques in identifying pro-inflammatory macrophages in atherosclerosis

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ABSTRACT

Atherosclerosis is an inflammatory condition characterized by severe arterial obstruction by the deposits of fatty plaques along the arterial walls. Pro-inflammatory macrophages contribute to the development of atherosclerotic plaques that underlie severe cardiovascular complications like myocardial infarction, making them an attractive diagnostic target. Given their high degree of selectivity, non-invasivity, and bioavailability, nanoparticles like N1177 and AuNP have recently entered the diagnostic landscape of atherosclerosis to improve tissue resolution in conventional imaging modalities like CT scans. Nevertheless, this approach has potential limitations of cytotoxicity and carcinogenic risks. Atherosclerosis accounts for one of the leading causes for morbidities worldwide which indicates an inherent need for equitable, accessible, and proactive diagnostic procedures. The purpose of this literature review is to evaluate macrophage-targeted nanotechnologies for *in vivo* diagnosis of atherosclerosis and their clinical potential. This literature review was conducted according to the PRISMA-S checklist through Ovid MEDLINE and Google Scholar.

INTRODUCTION

Atherosclerosis is a hallmark of ischaemic cardiovascular diseases and the leading cause of mortality worldwide, with an international prevalence for increased carotid plaque accumulation of 21.1% or nearly 813.76 million individuals, aged 30 to 79.[1] Atherosclerosis is a chronic inflammatory condition caused by the intramural retention of cholesterol-rich apolipoprotein B-lipoproteins sequestered in vulnerable sites on the arterial vasculature. Eventually, these lipoproteins aggregate into rupture-prone plaques, leading to cardiovascular complications.[2]

Pro-inflammatory macrophages are immune effector cells that phagocytize pathogens in their local environment. In atherosclerosis, macrophages initiate a maladaptive, non-resolving inflammatory response to plaque accumulation in the arterial wall.[3] Macrophages destabilize the extracellular matrix of arterial walls by ingesting cholesterol-rich lipoproteins, causing necrosis of the arterial wall. They secrete pro-inflammatory mediators and matrix-degrading proteases that specifically weaken the protective fibrous cap of the atheromatous core. Subsequently, tissue factor is released into the atherosclerotic plaques, accelerating intravascular thrombus formation and plaque rupture that underlies acute thrombotic vascular diseases, like myocardial infarction or cardiac failure.[4]

Accordingly, high densities of macrophages promote higher release of fibrous caps, and therefore correlate to increased susceptibility to ruptured plaques and thrombosis. Pro-inflammatory macrophages are reliable biomarkers for the prevalence of atherosclerosis, making them attractive targets for diagnostic imaging in clinical practice.[5] Therefore, effective noninvasive techniques for the early detection of pro-inflammatory macrophages are imperative to improving the diagnosis and characterization of atherosclerosis in clinical practice.

The use of nanoparticles in diagnostic imaging modalities is an emerging approach to non-invasively visualize macrophages at high-resolution in vivo. In particular, nanoparticle imaging agents can be targeted to specific sites of action given the differential distribution of nanoparticles in organs according to their size. For imaging macrophages, intermediate-sized nanoparticles (10–300 nm) are found to be preferentially distributed in the liver, spleen, and bone marrow, in addition to atherosclerotic plaques where macrophage recruitment occurs.[6] Further, nanoparticles are also credited for both increased bioavailability and half-life in circulation, offering an attractive opportunity for diagnostic imaging. Nanoparticles can stimulate, respond, and interact with target cells or tissues through controlled processes to produce the desired physiological responses while minimizing adverse effects.[7]

In the past, the gold standard for imaging pro-inflammatory macrophages in atherosclerosis has been intravascular ultrasound imaging. However, the procedure's invasivity, resolution limitations, and demanding time requirements underscore the need for alternative imaging techniques.[8] In

parallel, magnetic resonance imaging, which utilizes magnetic fields, and positron emission technology scans, which functionally assess the metabolism of radioactive biomarkers, have emerged as potential candidates for nanoparticle-based imaging due to their higher tissue resolution. However, numerous limitations associated with the negative contrast of superparamagnetic contrast agents, invasiveness, and time constraints limit their clinical translation. Another clinically robust technique is computed tomography (CT) scans, which operate through the combination of multiple X-ray images to produce cross-sectional images of localized tissue. Nevertheless, the use of CT scans in macrophage-based atherosclerosis diagnostics has practical limitations, as the high concentrations of nanoparticles that are required raises concerns of cytotoxicity, radiation exposure, and reduced cellular uptake.[9] Thus, the purpose of this review is to assess the literature on the efficacy of nanoparticle-based CT imaging for pro-inflammatory macrophages in atherosclerosis and analyze its potential for clinical applications.

METHODOLOGY

This literature review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension statement. An electronic literature search was performed consulting the Ovid MEDLINE and Google Scholar databases. A combination of keywords including ("atherosclerosis" OR "carotid artery disease*" OR "carotid plaque*") AND ("macrophage*" OR "monocyte*") AND ("CT scan*" OR "Computer Tomography" OR "diagnos*" OR "detection") AND ("nanoparticle*" OR "nanomedicine") was applied. Results were restricted to English articles published from inception to March 2022, strictly exclusive to peer-reviewed journals. Articles unrelated to nanosystems detection of macrophages in atherosclerosis were excluded, resulting in 21 relevant sources out of 185. Additionally, a grey literature search was conducted in March 2022 using the search string "macrophage-targeted nanomedicine for early detection of atherosclerosis". The first 30 results were selected and screened, producing 7 additional citations. From the 28 sources initially identified, 12 were selected for review.

RESULTS AND DISCUSSION

Generally, CT scans are associated with increased spatiotemporal and density resolutions, yet require contrast agents to compensate for density and resolution requirements. Barium sulfate-based contrast agents are conventionally used in CT scans, but are clinically limited by their toxicity, high internal scattering, reduced imaging time, and overall lack of specificity. From a clinical perspective, the CT scans offer increased feasibility for widespread clinical practice because of their cost-effectiveness and efficient turnaround times for imaging results.[10] Although an array of nanoparticle-imaging candidates for CT scans have been proposed, only N1177 nanoparticles and PEGylated Gold Nanoparticles have entered experimental trials. In comparison to other nanoparticle-imaging candidates for CT scans, N1177 nanoparticles and PEGylated Gold Nanoparticles have demonstrated minimal cytotoxicity, strong enhancement detected in CT scans for macrophage density, and appropriate organ distribution to advance towards *in vivo* studies.

N1177 Nanoparticles

6-Ethoxy-6-oxohexyl-3,5-bis(acetylamino)-2,4,6-triodobenzoate (N1177) nanoparticles are iodinated and experimentally found to be uptaken by macrophages.[11] Further, the effects of N1177 nanoparticles on phagocytic capacity and cytokine production were determined to be negligible, while N1177 nanoparticles produced high negative predictive values for eliminating the possibility of acute coronary syndromes, such as atherosclerosis.[12] Moreover, the integration of N1177 nanoparticles with multi-slice CT (MSCT) scans has enabled increased resolution in the identification of fibrous plaques as opposed to lipid-rich plaques in atherosclerosis. However, the clinical translation of N1177-MSCT is limited given a higher false-positive rate compared to angiograms and its non-negligible carcinogenic risk, both of which warrant future investigation. Specific to atherosclerosis, N1177-MSCT also has limitations in assessing the severity of coronary lesion for immediate stenosis. In clinical settings, the benefits of N1177 nanoparticles in atherosclerosis diagnosis could further support equitable access to early diagnosis and intervention for susceptible atherosclerosis patients.

PEGylated Gold Nanoparticles

Gold Nanoparticles (AuNP) have been used extensively in nanomedicine given their high stability, low toxicity, high X-ray attenuation coefficients, and extended half-life in circulation. According to Qin et al., fluorescein isothiocyanate-coated dendrimer-entrapped gold nanoparticles were determined to be non-cytotoxic at high concentrations of 300 μM and stable at biological pH, as well as have high hemocompatibility and an increased half-life in circulation on murine models.[13] Cumulatively, the use of AuNP produced increased quality of CT values compared to control murine trials, validating the increased resolution of CT imaging with AuNPs. Additionally, the PEGylation of AuNPs was determined to increase the half-life of the AuNPs in circulation, which further supports their integration into diagnostic imaging strategies. Nevertheless, there is a need for *in vivo* studies to validate the in vitro findings in support of implementing AuNP in CT scanning for pro-inflammatory macrophages in atherosclerosis.

CONCLUSION

To conclude, AuNPs and N1177 nanoparticles offer a promising frontier to broaden the diagnostic capabilities of CT imaging for early detection of macrophages involved in atherosclerosis. Nevertheless, further research is required to functionally validate these findings and determine optimal dosing for nanoparticles in clinical diagnostics. Ultimately, the integration of nanoparticles into CT imaging for atherosclerosis offers a revolutionary path in the development of nanomedicine and a leap towards greater health equity in reducing the cost of diagnostic imaging.

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Kevin Zhao is a MD/PhD candidate in the Department of Medical Sciences at McMaster University and a former *Meducator* contributor. His current research looks to investigate age-related changes to macrophage phagocytosis.

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References can be found on our website: meducator.org