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Promising Advances for Imaging Lung Macrophage Recruitment

Pulmonary hypertension (PH) contributes significantly to morbidity and mortality and has no curative therapies. Patients with World Health Organization group I pulmonary arterial hypertension (PAH) have improved survival as a result of targeted treatments, but 5-year survival remains low at 57% to 61% (1, 2), with a significant proportion ultimately requiring lung transplantation (3–5). Inflammation is being increasingly recognized as an important contributor to PAH development and progression (6). Therapies that reduce lung macrophage recruitment also reduce PH in animal models, further demonstrating the relevance of macrophages in PAH pathogenesis (7). Therefore, noninvasive biomarkers of lung macrophage recruitment and activity could help demonstrate the efficacy of macrophage-targeted therapies as well as enable investigations to understand how macrophages contribute to PAH development. Such biomarkers would also be applicable more broadly in multiple different lung diseases, including chronic obstructive pulmonary

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disease, idiopathic pulmonary fibrosis, and lung transplant rejection, among others.

Imaging is an attractive platform for developing macrophage biomarkers. Positron emission tomography (PET) is particularly attractive because it is inherently quantitative. Nearly any biological product or chemical entity can be transformed into a PET tracer by radiolabeling with a positron emitter, providing great flexibility in interrogating molecular targets. Administered in very small amounts (nanogram mass amounts or less), PET tracers in general have a large safety margin. Recent advances in PET scanner hardware, including digital PET scanners and total body scanners that are long enough to image the entire body from head to toe within minutes, will provide improved sensitivity and spatial resolution that can enable improved characterization of novel PET tracers in the lungs in humans (8, 9). Together, these features and advancements make PET ideally suited for interrogating any number of molecular targets, including tracking macrophages. As such, a number of PET tracers have been developed for imaging targets enriched in or specific for monocytes and macrophages in the lungs, including the translocator protein (10), cysteine cathepsins (11), and chemokine receptor 2 (12).

In this issue of the *Journal*, Park and colleagues (pp. 95–106) describe a tracer, ^{68}Ga-NOTA-mannosylated serum albumin (^{68}Ga-NOTA-MSA), for PET imaging of a marker of M2 polarized macrophages, the mannose receptor (13). The authors demonstrated the potential utility of this imaging approach in a preclinical model of PH and in a small proof-of-concept study in humans. For this evaluation, the authors first verified increased transcription of macrophage activation factors in the established monocrotaline rat model of PH at the same time points evaluated by imaging. They then demonstrated that ^{68}Ga-NOTA-MSA lung uptake in this model correlated highly with the degree of macrophage infiltration. This uptake was partially blockable with mannan, suggesting that the lung uptake was due to specific binding.

The authors further demonstrated in a small proof-of-concept study that ^{68}Ga-NOTA-MSA lung uptake was increased in five patients with group I PAH but not in healthy control subjects or in an additional five patients with World Health Organization Group II left heart disease–related PH. These exciting preliminary results suggest the potential utility of ^{68}Ga-NOTA-MSA to detect macrophages associated with PAH. Although macrophage recruitment is less well studied in group II PH, macrophages have been demonstrated to drive PH development in the context of heart disease (7). Therefore, these results suggest the possibility of differences in macrophage phenotypes in these two PH populations that warrants further investigation.

Common factors that can confound the interpretation of lung PET tracer uptake as specific include the high relative fractional blood volume in the lungs and alterations in blood flow. The large blood volume in the lungs can result in a large contribution to lung activity from tracer in the blood, making it difficult to measure changes in uptake due to the targeted process. Changes in blood flow can also affect the amount of tracer delivered or cleared over time. In PAH, however, these variables are less likely to confound the interpretation of increased lung tracer uptake as specific. In this study, ^{68}Ga-NOTA-MSA uptake correlated highly with macrophage recruitment and increasing arterial hypertrophy, the latter of which would lead to lower blood volumes and thus a lower contribution from blood to the total measured lung activity. Inflammation tends to increase blood flow, at least initially, in many models. However, again because of the progressive arterial hypertrophy in this model, increased pulmonary blood flow is not the most likely explanation for the increased lung uptake of ^{68}Ga-NOTA-MSA at these time points. Decreases in blood flow due to progressive vascular proliferation could also lead to nonspecific retention of the tracer as a result of delayed tracer clearance, which may explain the residual uptake seen after administering mannan. Independently measuring the effects of blood flow and blood volume on delivery and retention of ^{68}Ga-NOTA-MSA in the lungs would provide additional supportive data demonstrating the specificity of this tracer for imaging mannose receptor–expressing macrophages in this model. Similarly, in the patient study, the ^{68}Ga-NOTA-MSA lung uptake seen in the patients with group I PAH was less likely to be confounded by blood activity, as Vcs are reduced in these patients (14).

In conclusion, this study presents promising initial data demonstrating that ^{68}Ga-NOTA-MSA may be a useful marker of M2 polarized macrophages in PAH. Further investigations to validate the lung uptake of this tracer as a marker of M2 macrophages in patients with PAH and other relevant diseases are warranted. ■

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