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Protease activity sensors enable real-time treatment response monitoring in lymphangioleiomyomatosis

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Shareable abstract (@ERSpublications)
Nanoparticles that noninvasively measure the activity of proteases in the lungs enable real-time monitoring of disease progression and therapeutic response in a mouse model of lymphangioleiomyomatosis https://bit.ly/3z4cnAh

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Abstract

Background Biomarkers of disease progression and treatment response are urgently needed for patients with lymphangioleiomyomatosis (LAM). Activity-based nanosensors, an emerging biosensor class, detect dysregulated proteases *in vivo* and release a reporter to provide a urinary readout of disease. Because proteases are dysregulated in LAM and may directly contribute to lung function decline, activity-based nanosensors may enable quantitative, real-time monitoring of LAM progression and treatment response. We aimed to assess the diagnostic utility of activity-based nanosensors in a pre-clinical model of pulmonary LAM.

Methods *Tsc2*-null cells were injected intravenously into female nude mice to establish a mouse model of pulmonary LAM. A library of 14 activity-based nanosensors, designed to detect proteases across multiple catalytic classes, was administered into the lungs of LAM mice and healthy controls, urine was collected, and mass spectrometry was performed to measure nanosensor cleavage products. Mice were then treated with rapamycin and monitored with activity-based nanosensors. Machine learning was performed to distinguish diseased from healthy and treated from untreated mice.

Results Multiple activity-based nanosensors (PP03 (cleaved by metallo, aspartic and cysteine proteases), $p_{adjusted}<0.0001$; PP10 (cleaved by serine, aspartic and cysteine proteases), $p_{adjusted}=0.017$)) were differentially cleaved in diseased and healthy lungs, enabling strong classification with a machine learning model (area under the curve (AUC) 0.95 from healthy). Within 2 days after rapamycin initiation, we observed normalisation of PP03 and PP10 cleavage, and machine learning enabled accurate classification of treatment response (AUC 0.94 from untreated).

Conclusions Activity-based nanosensors enable noninvasive, real-time monitoring of disease burden and treatment response in a pre-clinical model of LAM.