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Title

BNP is Selectively Produced by Amyloid-Associated Cardiomyocytes at Amyloid Border Zones in Patients with Cardiac Amyloidosis

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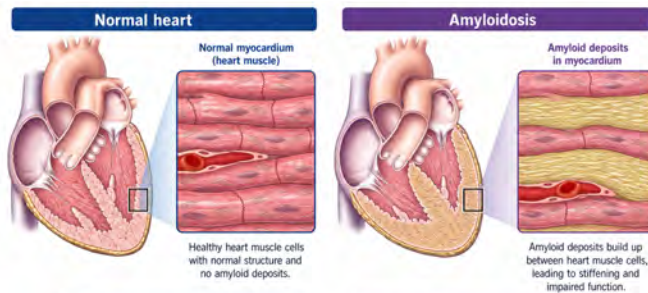
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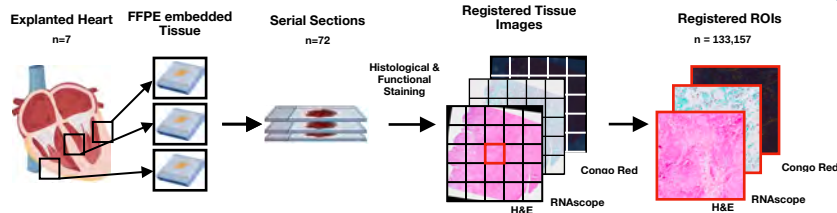
INTRODUCTION

Extracellular deposition of misfolded proteins is a defining feature of amyloid diseases, yet how these deposits alter the function of neighboring cells remains poorly understood. Cardiac amyloidosis is among the most clinically consequential forms, in which amyloid accumulation in the myocardium leads to restrictive cardiomyopathy and progressive heart failure. The disease affects an estimated 15-30% of patients with heart failure with preserved ejection fraction, underscoring its prevalence and the urgent need for mechanistic insight^{5,6}.

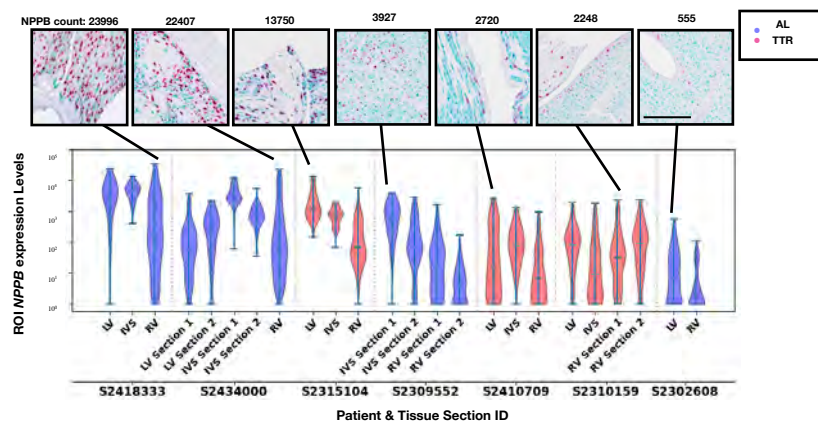
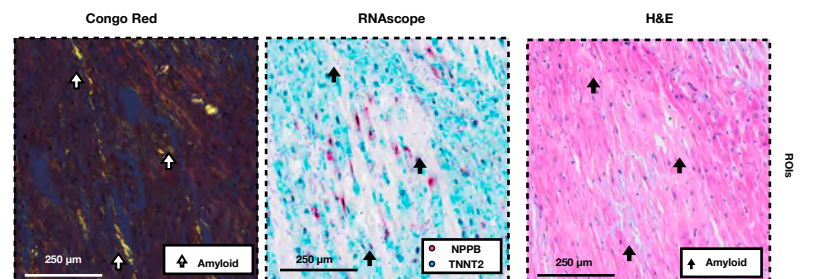
B-type natriuretic peptide (BNP) and its amino-terminal fragment (NT-proBNP), encoded by **NPPB**, are the primary biomarkers used to stage disease severity and monitor treatment response in cardiac amyloid. They are thought to reflect cardiomyocyte stress, but whether this results from direct proteotoxicity of amyloid fibrils or from mechanical stress by extracellular deposits remains unclear.



Spatial Heterogeneity of NPPB Expression

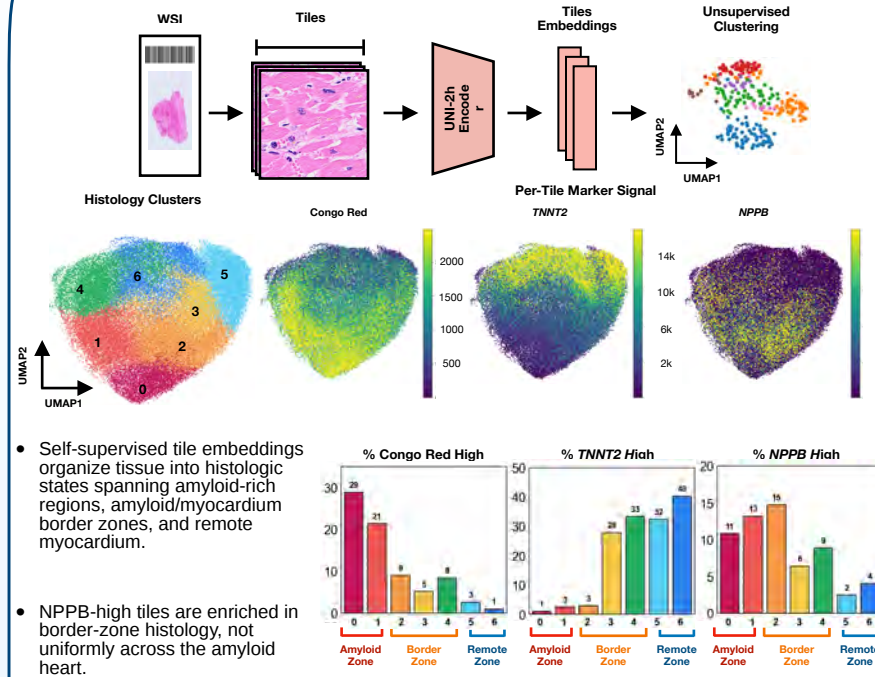


- Serial-section registration maps amyloid deposits, myocardium, and NPPB signal in matched tissue regions.

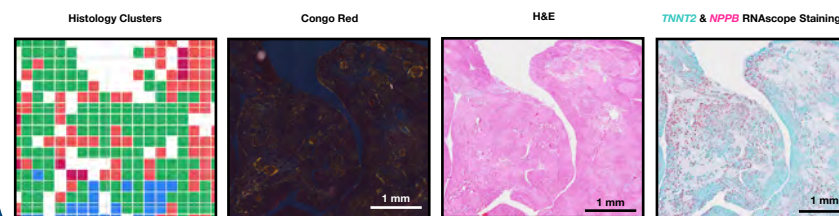


- NPPB is not uniformly expressed across amyloid myocardium. Instead, NPPB-positive regions appear as focal hotspots near Congo Red-positive deposits.

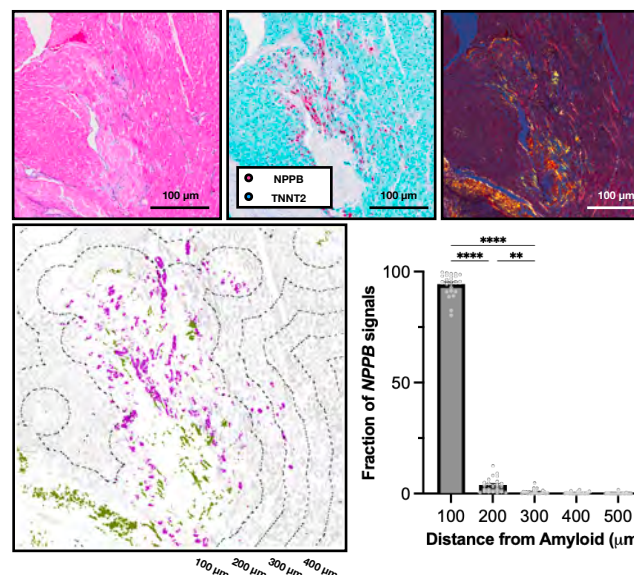
Histology Embeddings Identify NPPB-High Amyloid Border Zones



- Self-supervised tile embeddings organize tissue into histologic states spanning amyloid-rich regions, amyloid/myocardium border zones, and remote myocardium.
- NPPB-high tiles are enriched in border-zone histology, not uniformly across the amyloid heart.

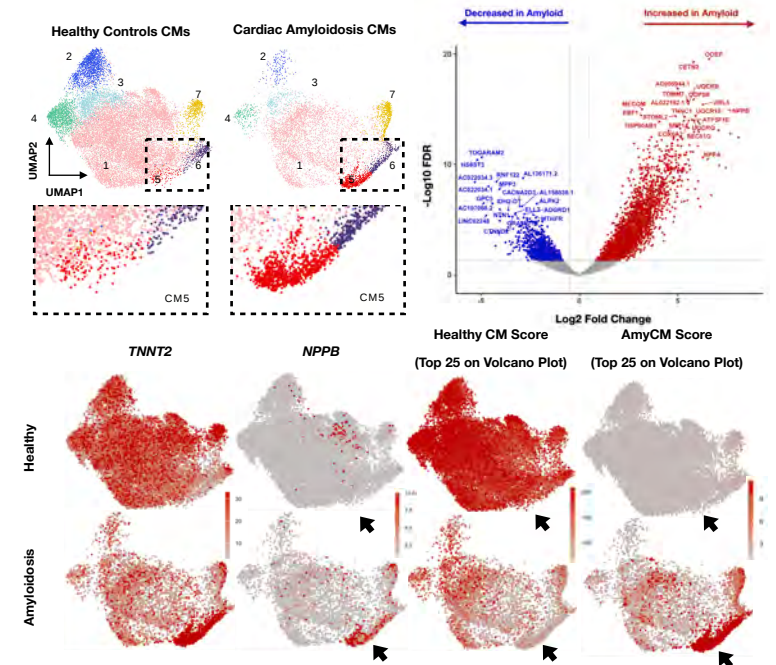


NPPB RNAscope Signal Enriched near Amyloids

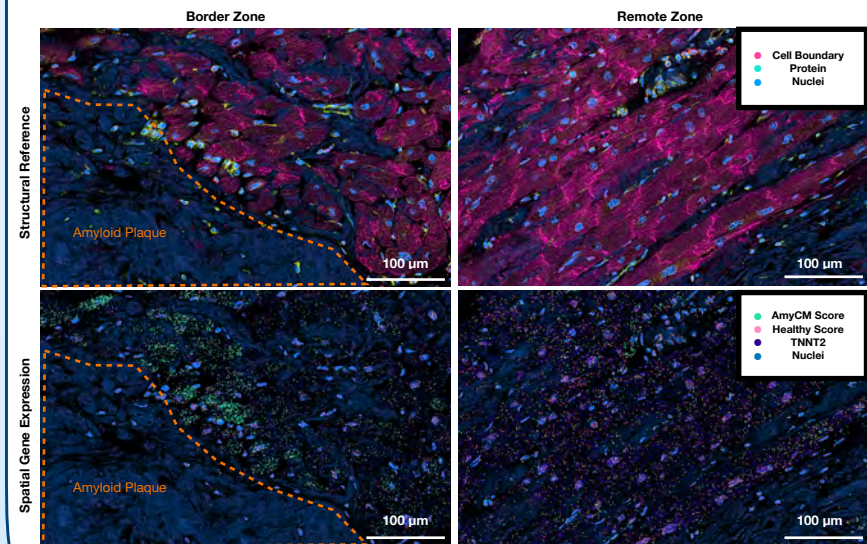


- Distance mapping shows that NPPB signal is sharply enriched near Congo Red-positive amyloid deposits.
- More than 90% of NPPB signal falls within ~100 µm of amyloid, consistent with a narrow amyloid-myocardium border zone.

Transcriptional and Spatial Characterization of Amyloid Stress cardiomyocytes



- snRNA-seq identifies an amyloid-enriched cardiomyocyte state marked by NPPB/NPPA and stress-adaptive transcriptional programs.
- These Amyloid Stress Cardiomyocytes show increased metabolic and contractile/mechanical stress signatures.



- Xenium spatial transcriptomics validates that the Amyloid Stress CM score localizes to amyloid border zones, while remote myocardium remains more control-like.

Conclusion

- Amyloid injury is spatially heterogeneous.** Cardiac amyloid deposits create discrete amyloid-myocardium border zones rather than uniform myocardial activation.
- NPPB/BNP is a border-zone signal.** Over 90% NPPB signal is concentrated within ~100 µm of amyloid deposits, implicating local amyloid-associated cardiomyocytes as a major source.
- Border-zone cardiomyocytes adopt an Amyloid Stress CM state.** NPPB+ cardiomyocytes activate metabolic and mechanical/contractile stress programs, linking local amyloid architecture to the systemic BNP/NT-proBNP biomarker.