Mechanosensation regulates myeloid cell function

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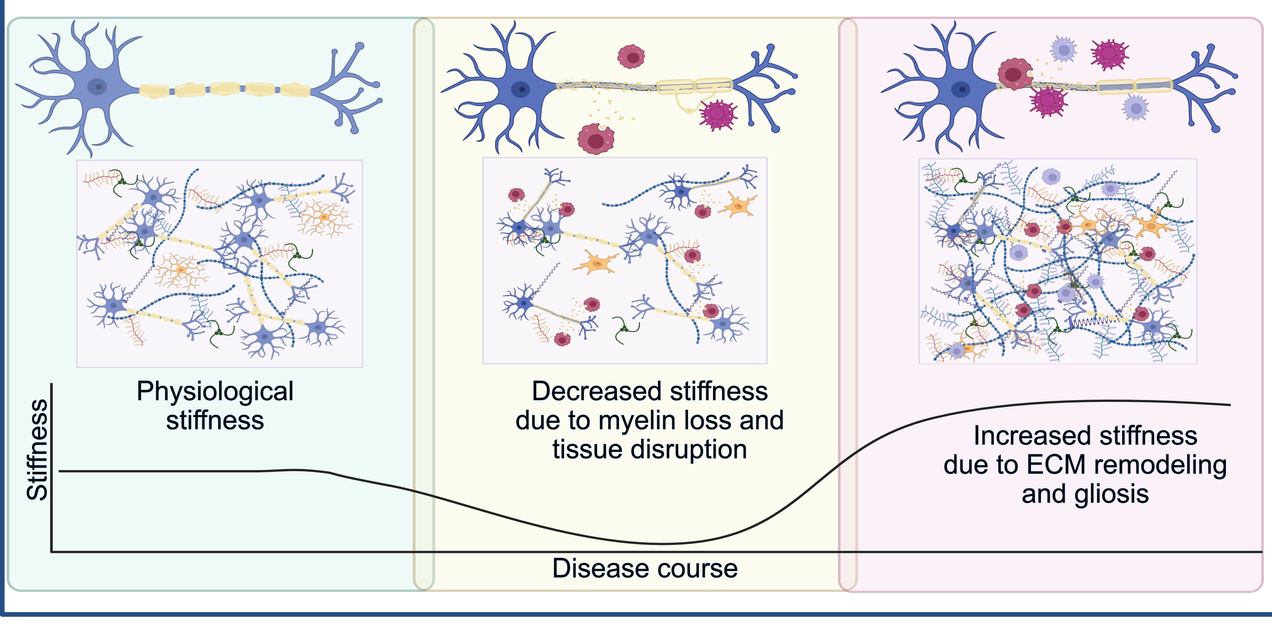
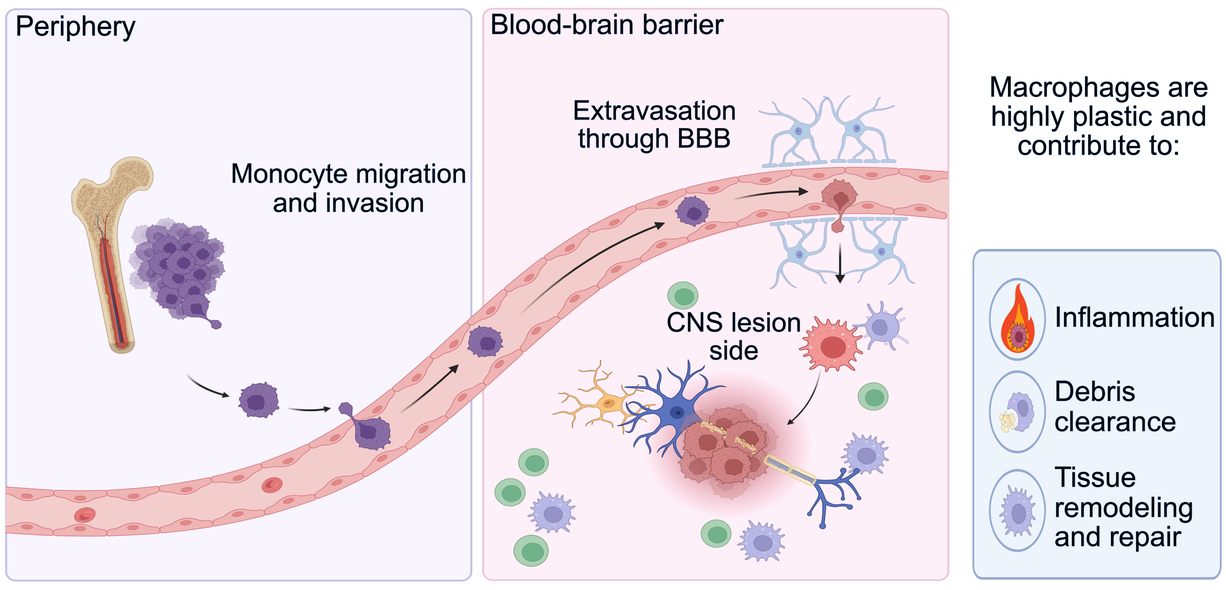
INTRODUCTION

Tissue stiffness in MS changes dynamically over time



Why we focus on myeloid cells in the CNS

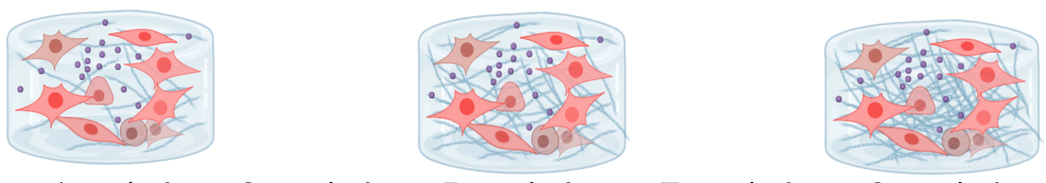
In MS, breakdown of the blood–brain barrier permits peripheral monocyte infiltration into the CNS, where they differentiate into macrophages. These cells accumulate in lesions and drive both tissue damage and repair.



HYPOTHESIS & APPROACH

We use a tunable 3D hydrogel system to model a range of tissue stiffnesses in vitro. This system allows us to investigate how stiffness regulates myeloid cell phenotypes and mechanosensitive signaling pathways relevant to MS.

We hypothesize that increasing tissue stiffness in MS-relevant conditions alters myeloid cell polarization and associated molecular response mechanisms.



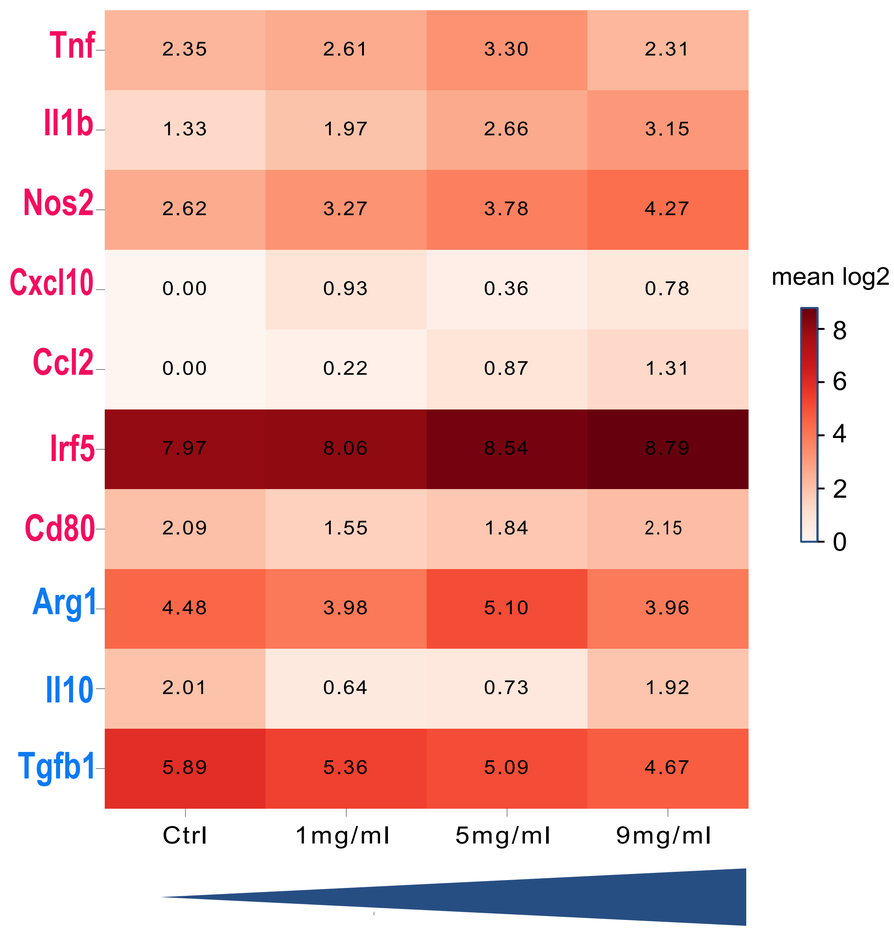
2D control → Stiffness/ Collagen concentration

Polarization

Day 0 — MCSF — Day 5 — Cytokines — Day 7

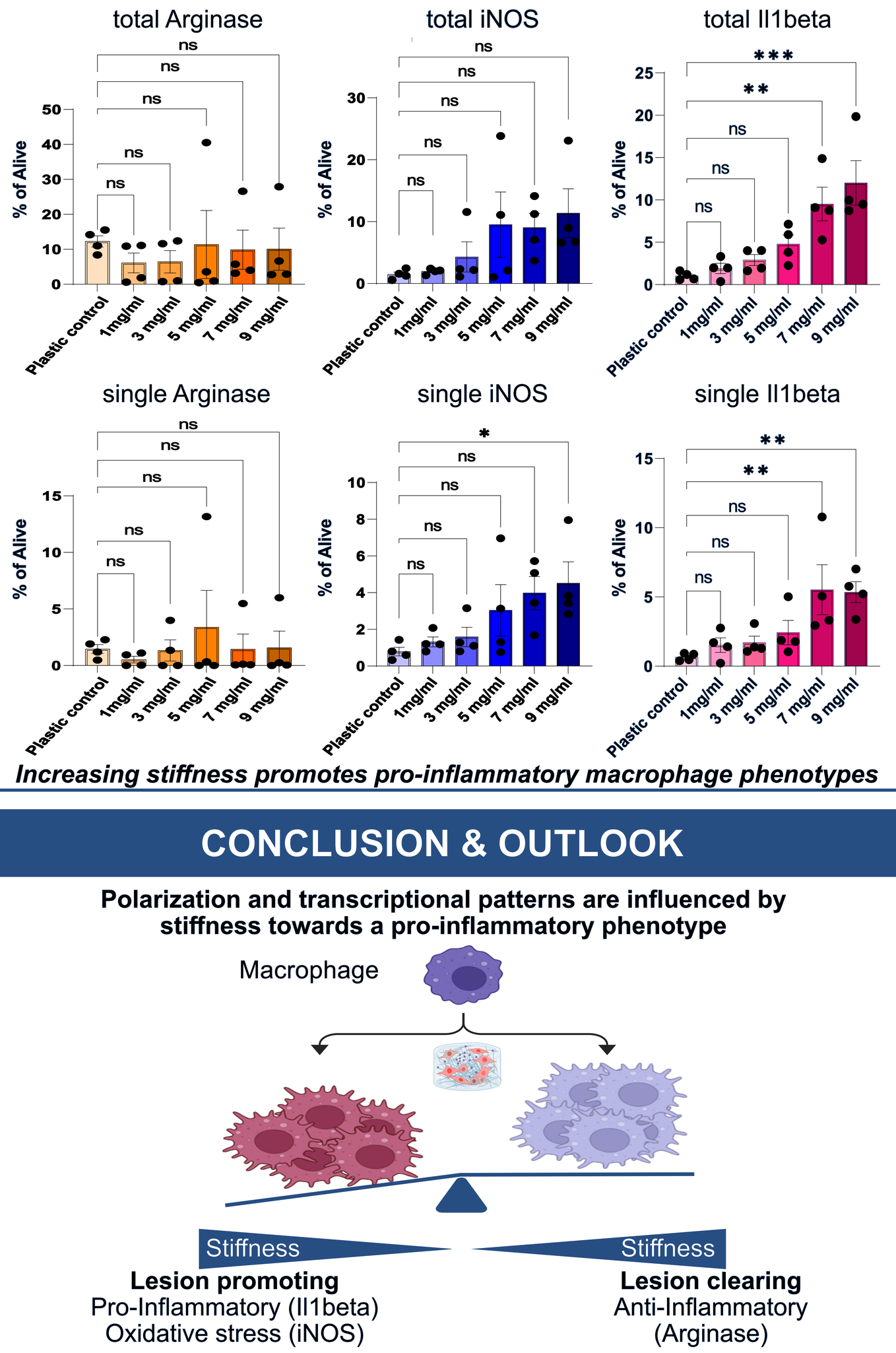
GmCSF, IL4, TNFa,INFy, TGFb

POLARIZATION & MECHANOSENSING PATTERNS



- ***Mechanical cues trigger distinct transcriptional responses in myeloid cells***
- ***Stiffness regulates broad mechanosensitive gene expression programs***

IMPACT OF INCREASING STIFFNESS ON MYELOID CELL FUNCTION



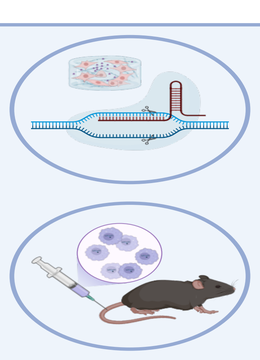
Increasing stiffness promotes pro-inflammatory macrophage phenotypes

CONCLUSION & OUTLOOK

Polarization and transcriptional patterns are influenced by stiffness towards a pro-inflammatory phenotype

Lesion promoting
Pro-Inflammatory (Il1beta)
Oxidative stress (iNOS)

Lesion clearing
Anti-Inflammatory
(Arginase)



Identify key regulators of macrophage mechanosensation and mechanotransduction using pooled CRISPR screening in 3D hydrogel cultures

Assess the functional relevance of top candidates in a chronic MS mouse model

REFERENCES

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