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The disease: Familial Mediterranean Fever

Type: Hereditary, auto-inflammatory disease

Genetics: Mutations in the Mediterranean fever gene (MEFV), encoding the Pyrin protein

Synonyms: periodic peritonitis, periodic fever and recurrent polyserositis

Triggers: physical activity, infections and stress in general

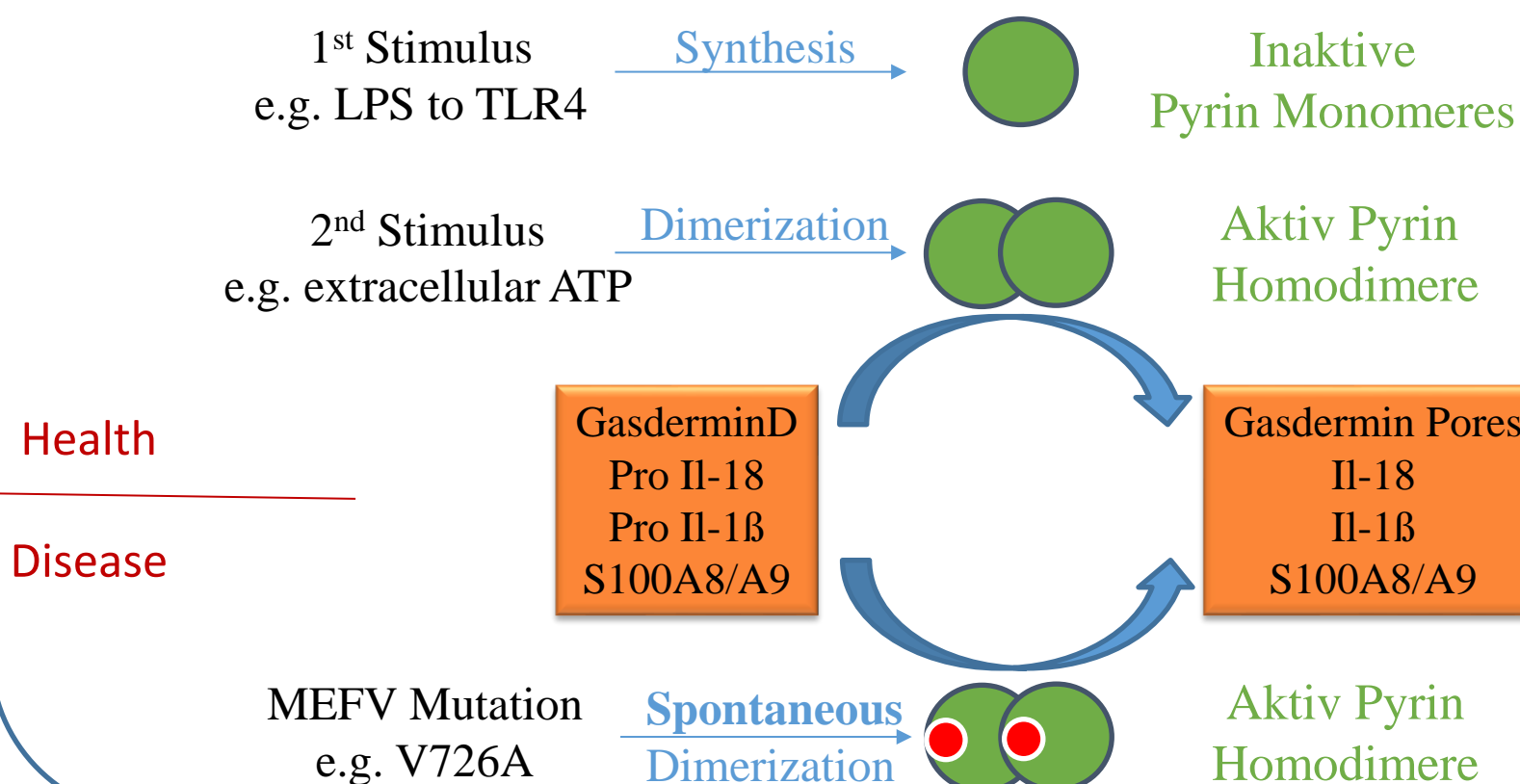
Somatic complications: amyloidosis or vasculitis-related diseases

Psychological complications: reduced quality of life and social participation

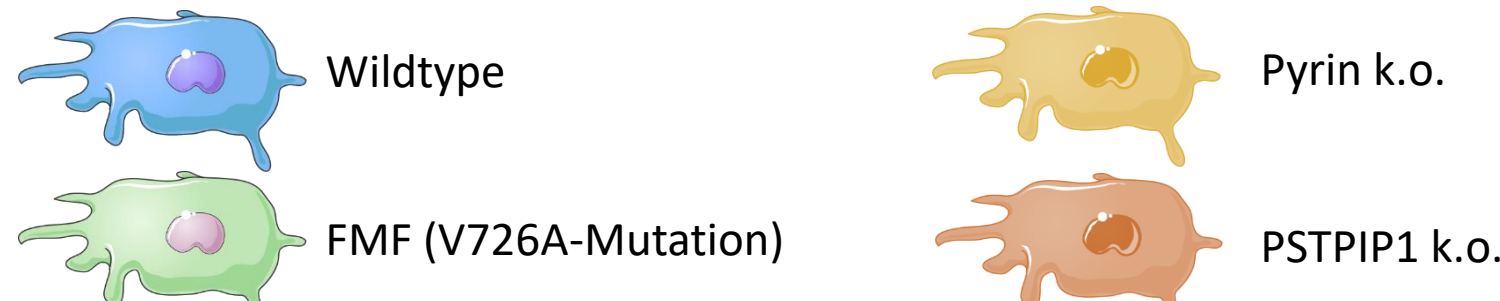
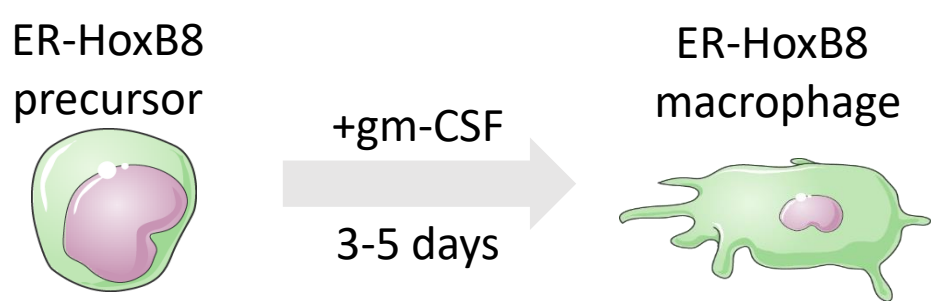
The goal of our work:

In this study we seek to shed light on the role of **macrophages** in the pathophysiology of **FMF** using the **ER-HoxB8 cell system** carrying the disease-causing mutation **V726A**, a **Pyrin** knockout and a **PSTPIP1** knock out, causing the **PAPA-Syndrom**.

The mutation: V726A in the pyrin inflammasome

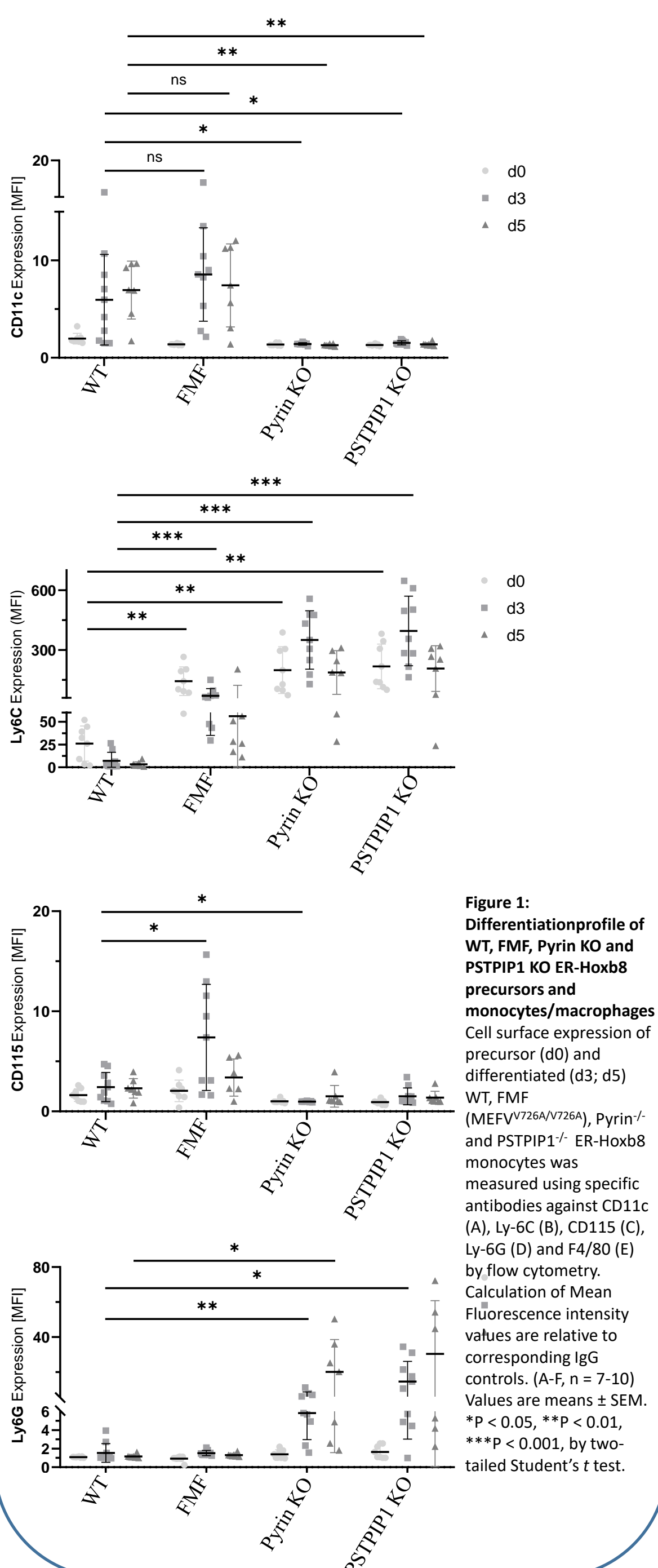


The HoxB8 cell system

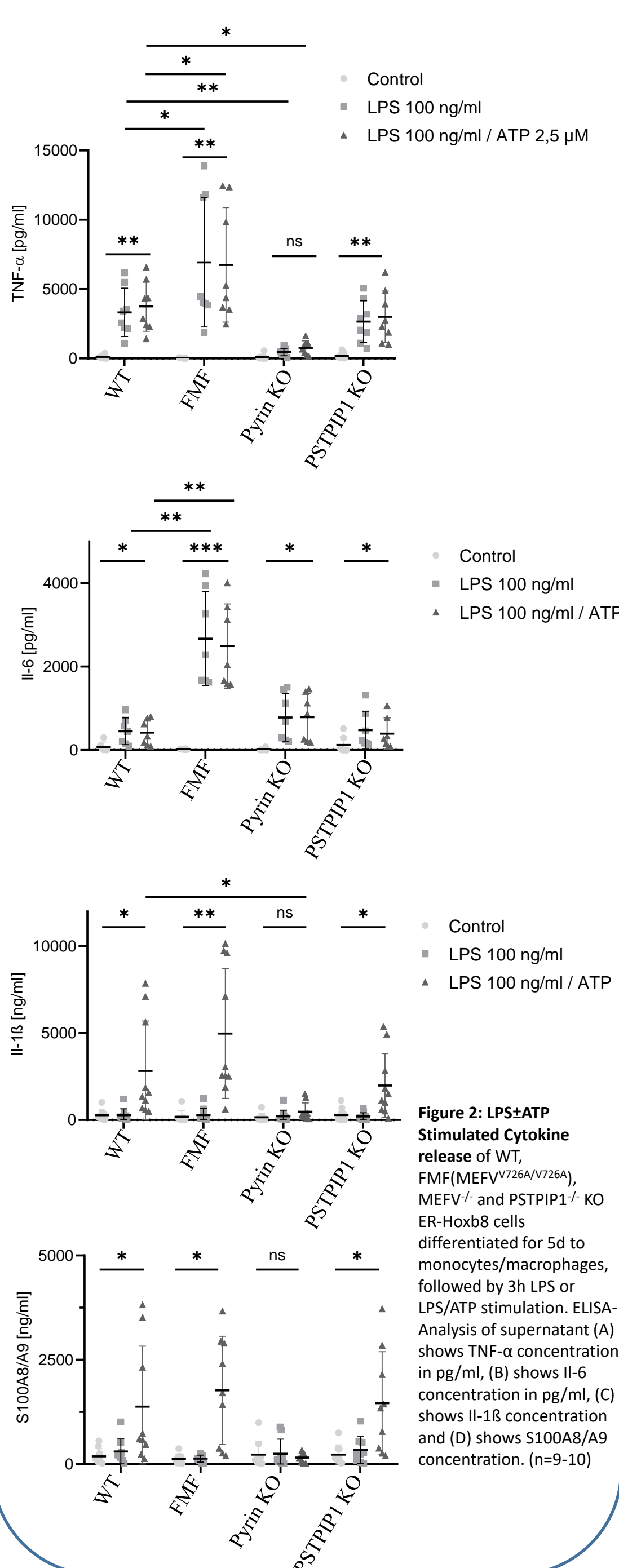


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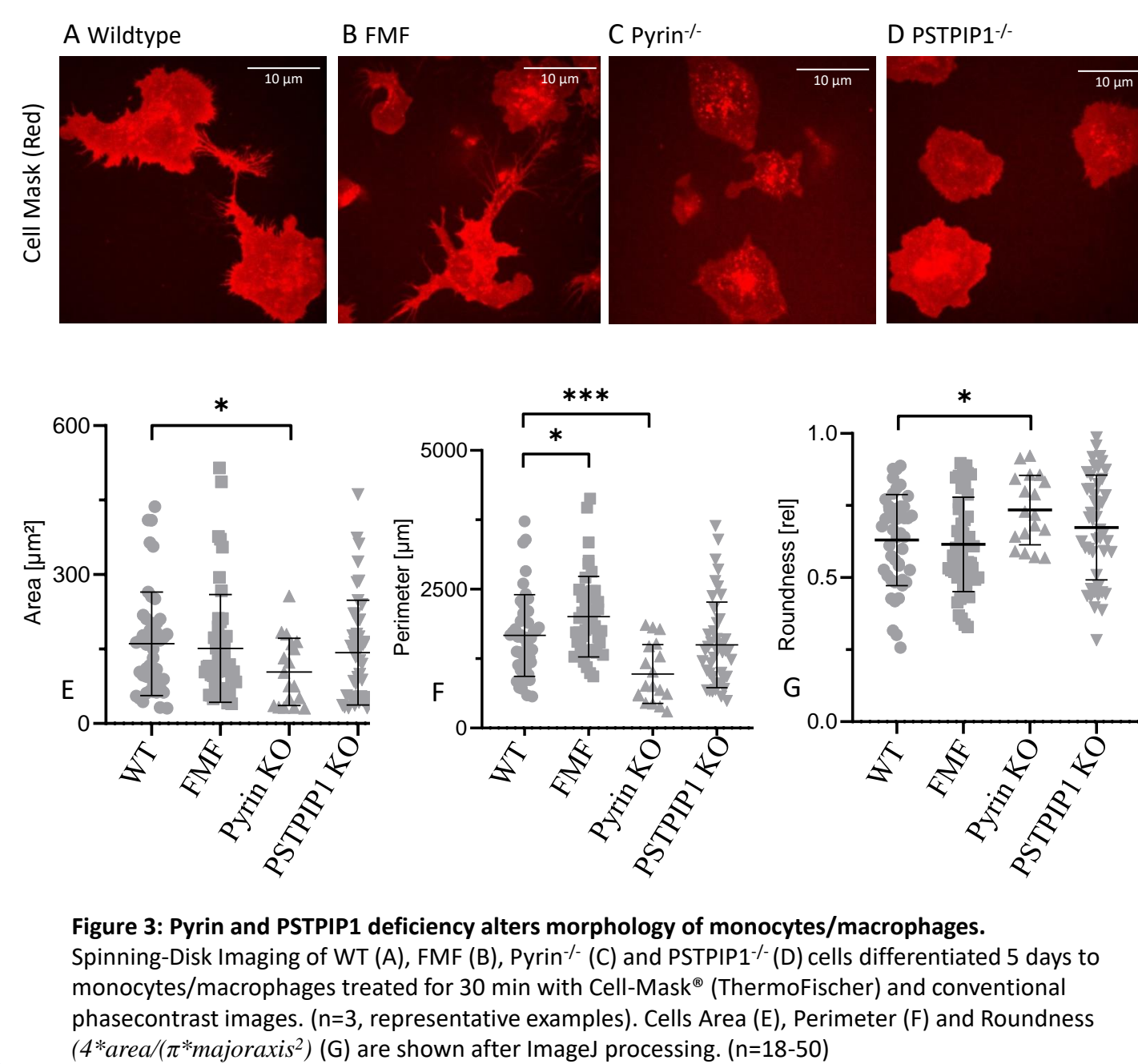
Differentiation



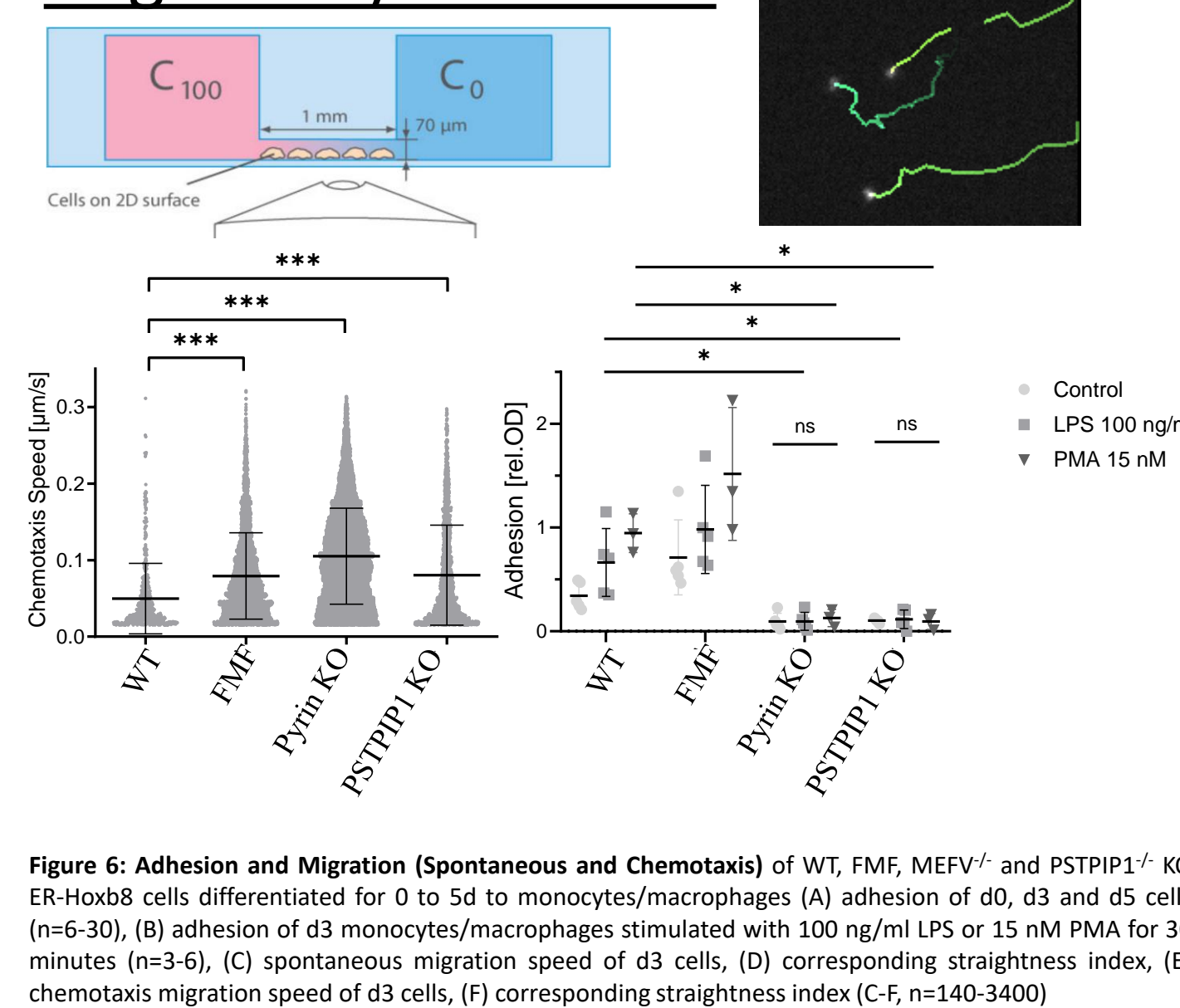
Secretion



Morphology



Migration / Adhesion



3

Summary

- Pyrin mutation, KO or PSTPIP1 KO results in unspecific cell differentiation
- FMF macrophages show an increased susceptibility towards inflammatory stimuli, while the Pyrin k.o. show a decrease. This effect is not limited to inflammasome-dependent cytokines
- FMF monocytes show increased adhesion, longer protrusions, and a higher speed of motion
- Pyrin k.o. monocytes show a decreased adhesion and faster movement speed but have a smaller and rounder phenotype than wildtype

Conclusion

The effects of Pyrin mutation, KO or PSTPIP1 KO are not limited to inflammasome-dependent effects, possibly resulting from an altered differentiation

Outlook

- Investigation of the role of small GTPases (e.g. RhoA, Rac1, CDC42)
- Utilization of established therapeutics
- Utilization of GASDERMIN D Blockers
- Extension towards human samples