

Linking Antiviral Immune Sensing to Microglial Inflammatory and Homeostatic Dysregulation in Alzheimer's Disease via OAS1

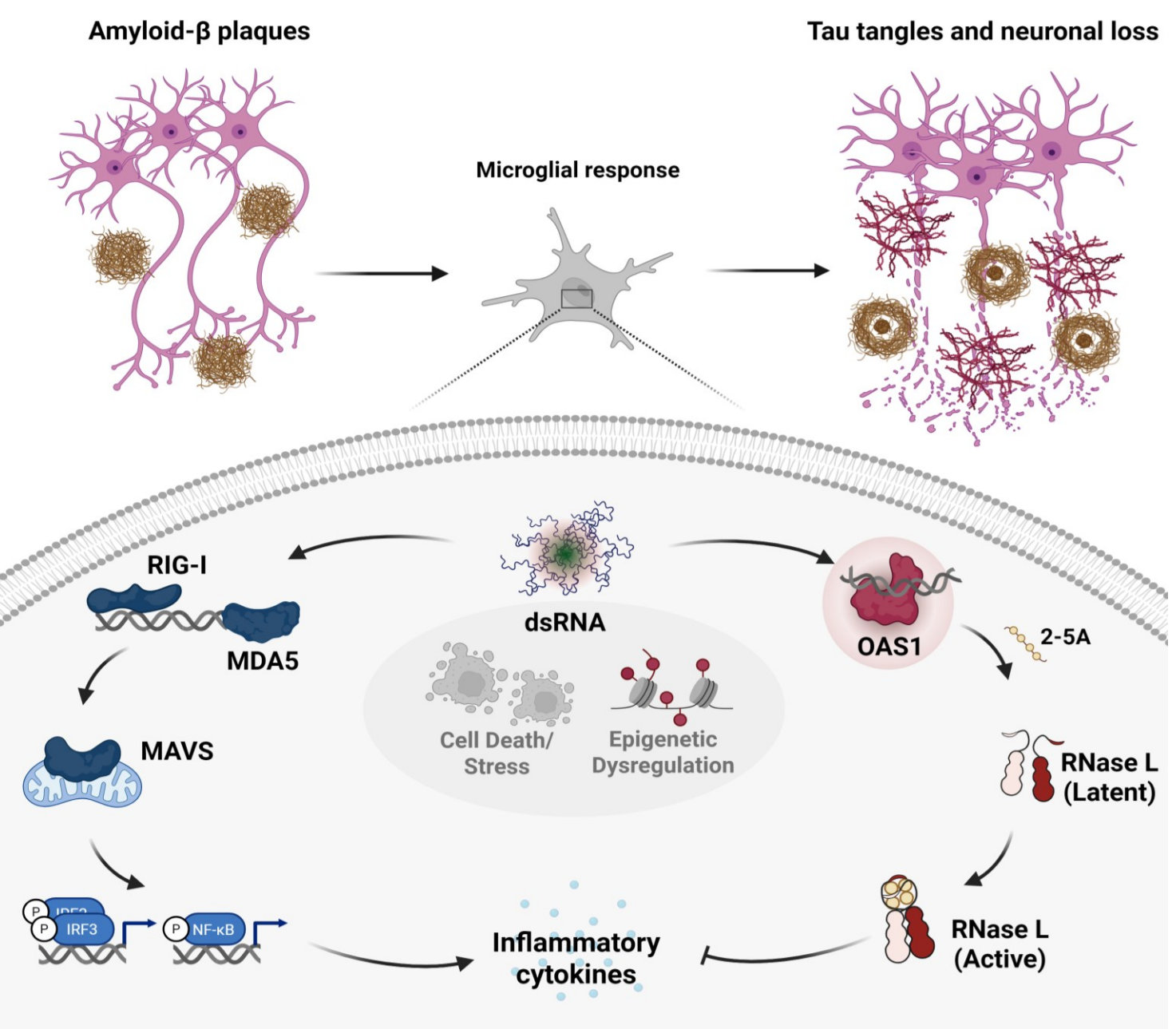
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INTRODUCTION

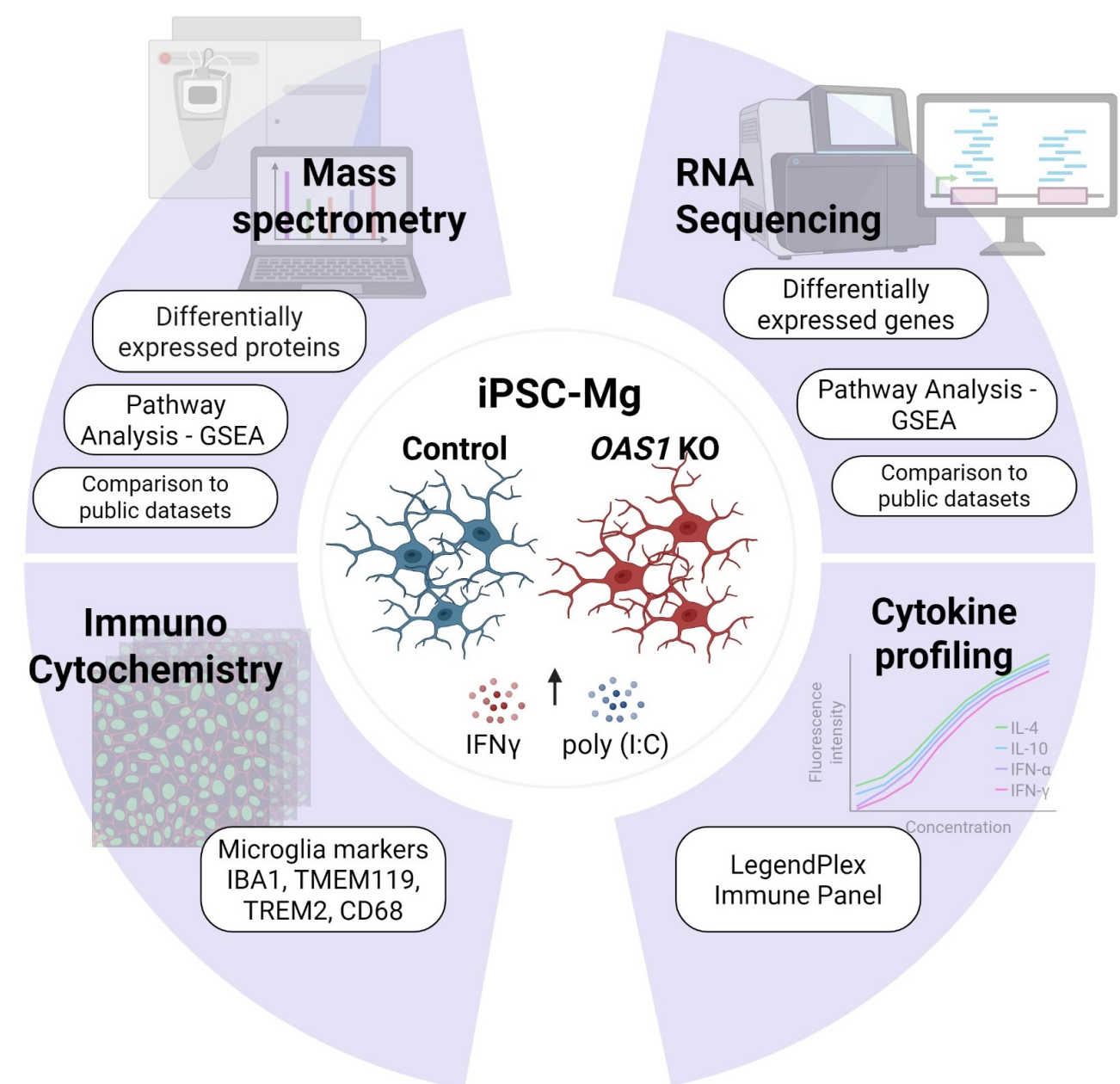
Interferon-Responsive OAS1 Acts as Nucleic Acid (dsRNA) sensor

Neuroinflammation in Alzheimer's disease (AD) is shaped by **interferon signalling** pathway which regulates how microglia respond to disease-associated cues and, when dysregulated has been shown to have adverse effects on the disease progression^{1,2}. We previously identified the interferon-responsive gene, **OAS1**, as a **genetic risk factor** for AD with decreased expression, and found that OAS1 limits the pro-inflammatory responses of microglia during interferon activation^{3,4}. OAS1 is an enzyme that is activated upon **dsRNA binding** and activates RNase L, which degrades viral and host RNA, and inhibits viral replication⁵.



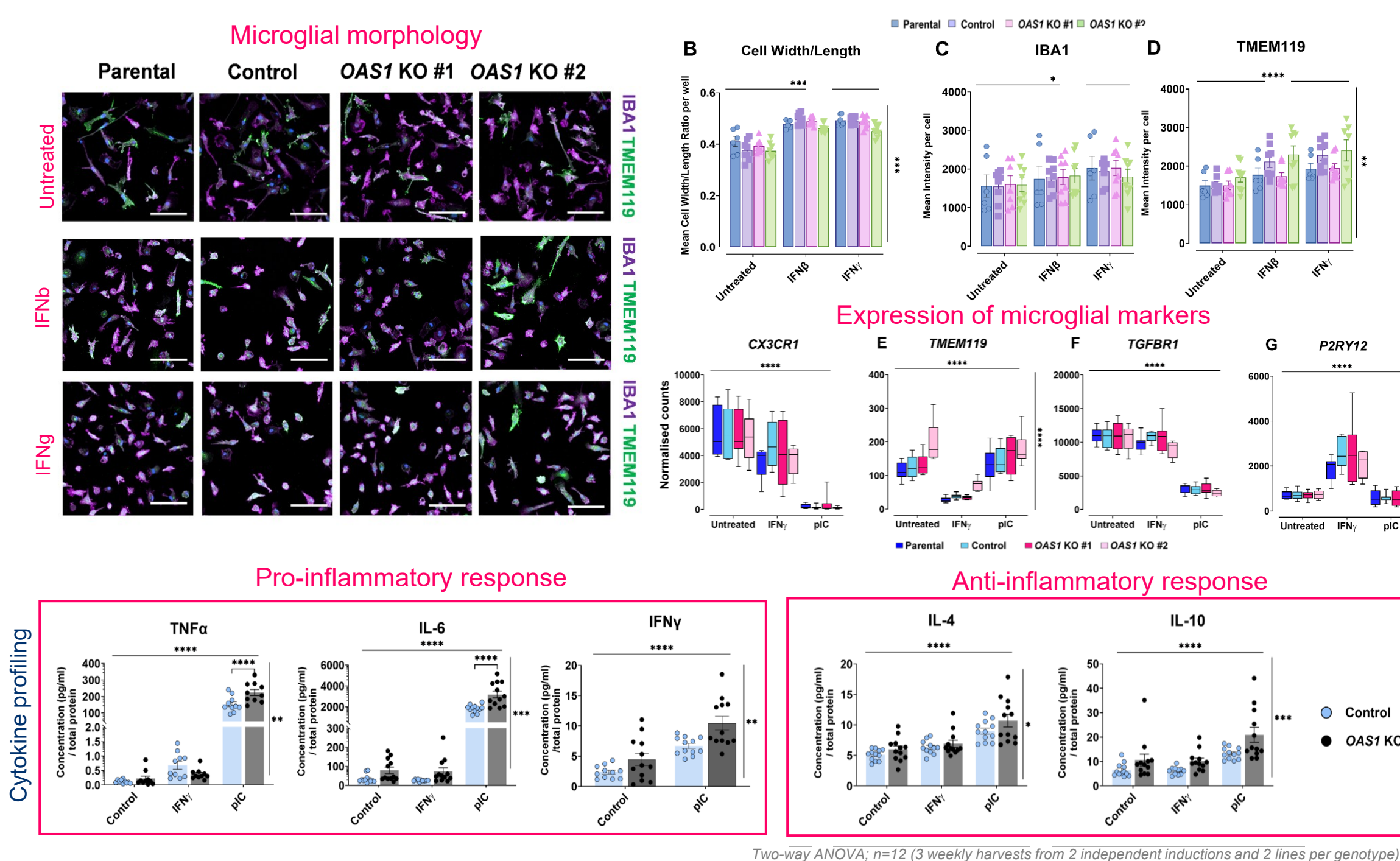
AIM: to understand molecular and cellular mechanisms by which OAS1 and anti-viral responses modulate the AD progression through microglia

METHODS

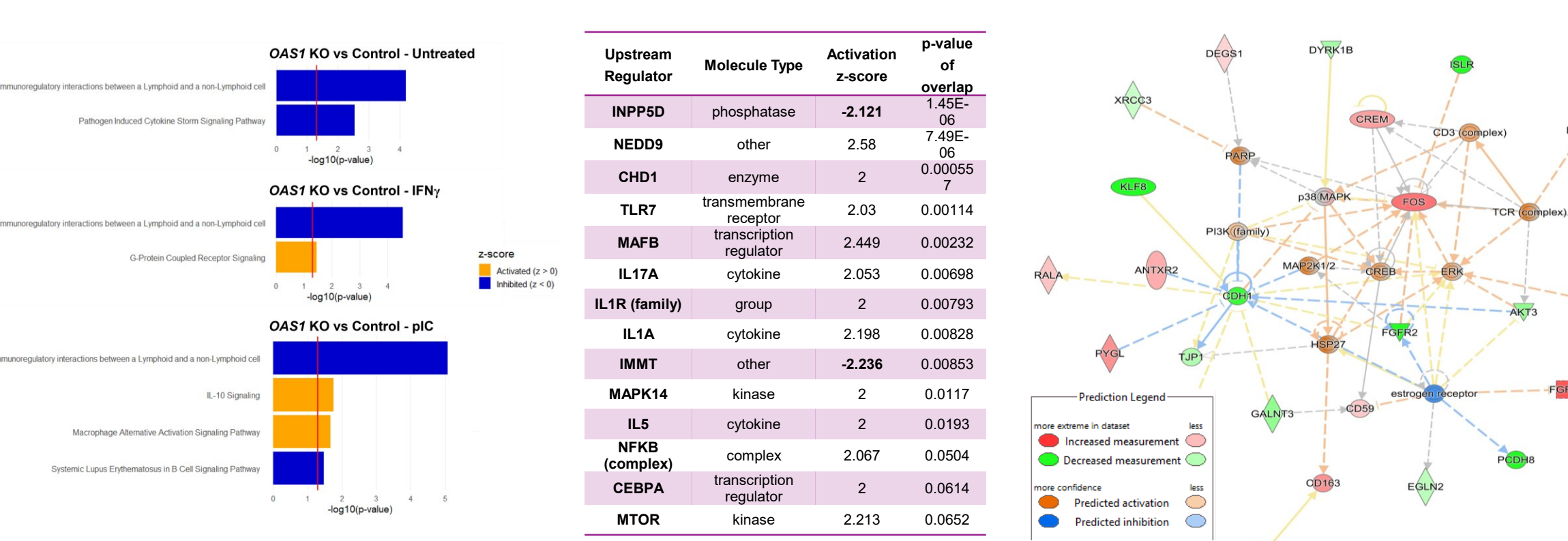


RESULTS

Loss of OAS1 Leads to Exacerbated Pro-inflammatory Responses in iPSC-microglia with dsRNA Stress

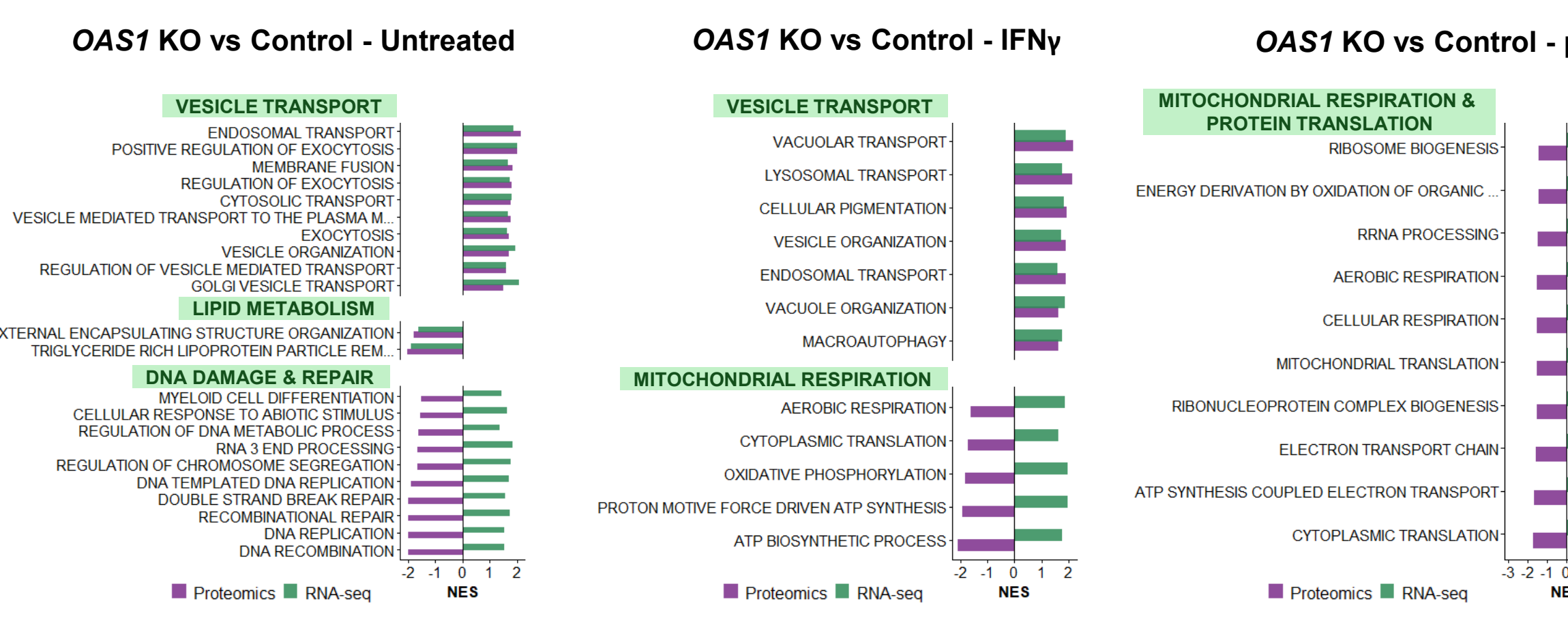


Altered inhibitory immunoreceptor expression accompanies dysregulated inflammatory response in OAS1 KO microglia

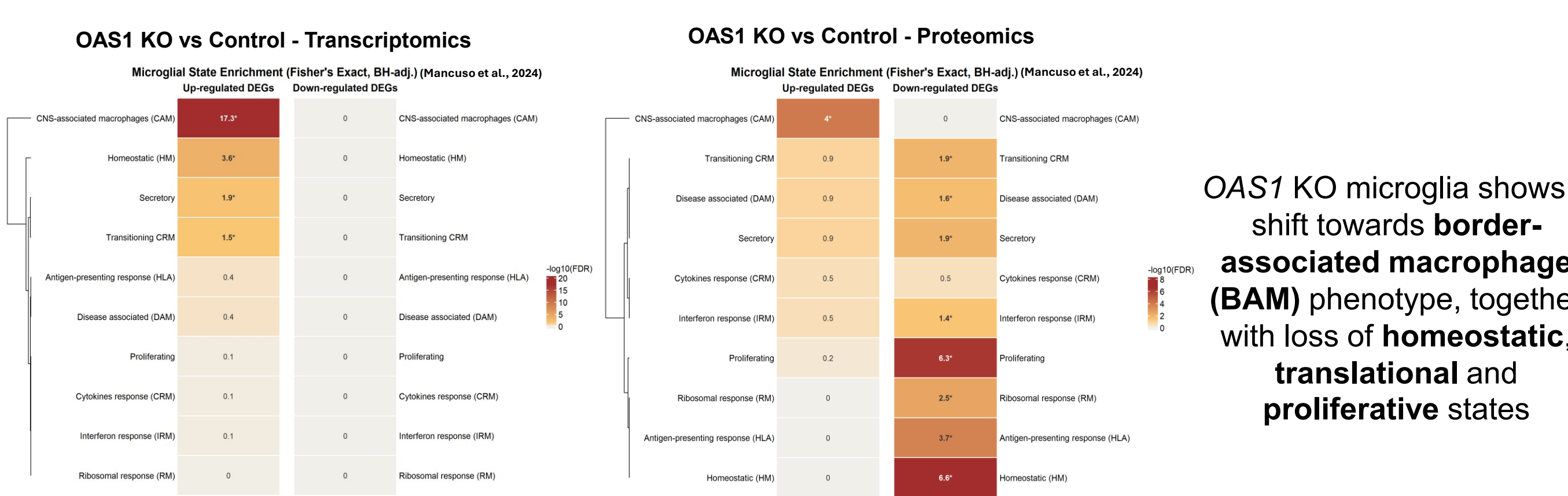


Transcriptomic results collectively suggest that OAS1 acts as a regulator of immunomodulatory responses, by balancing the immunosuppressive activities via the **LILRB – INPP5D** signalling axis

OAS1 Loss Reveals Stimulus-Dependent Contrasting Transcriptomic and Proteomic Signatures of Mitochondrial Respiration And Translation

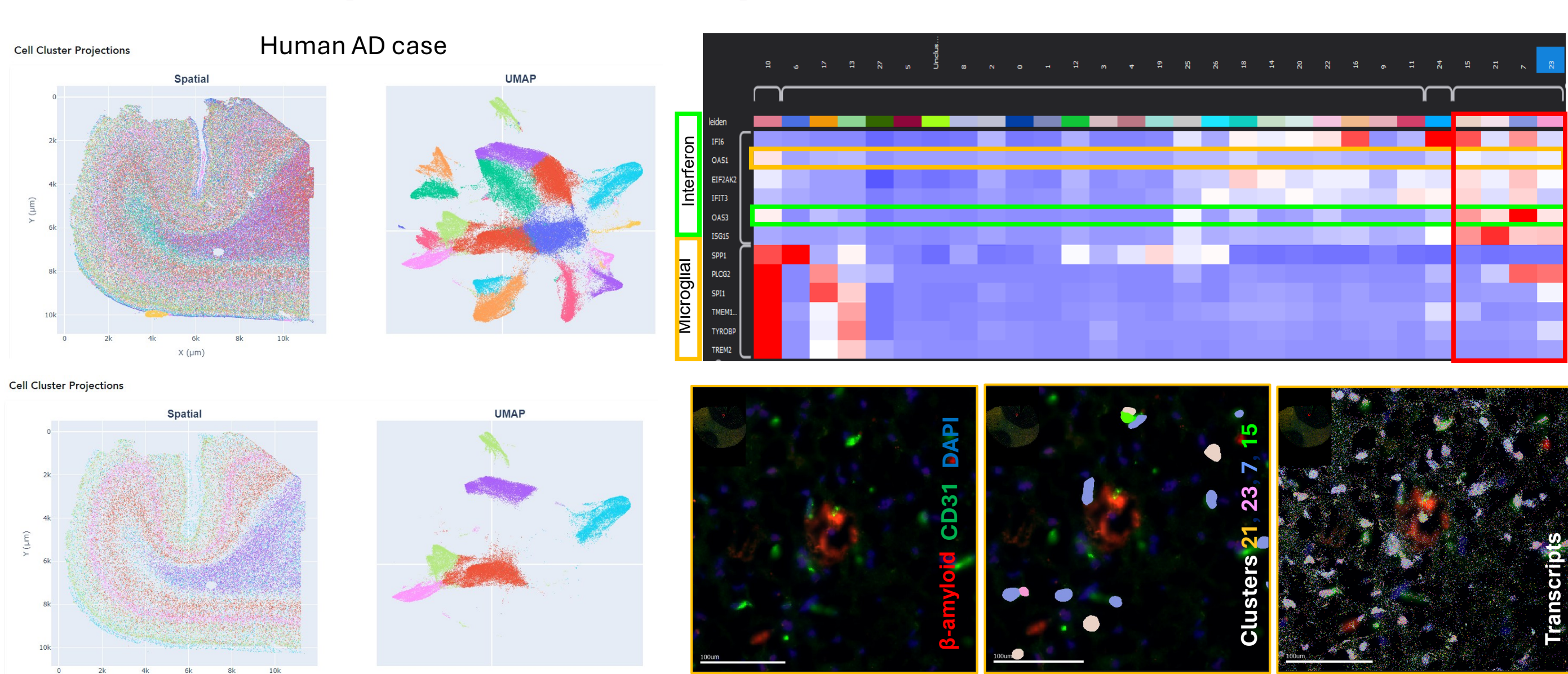


Transcriptomic and Proteomic Profile of OAS1 KO Microglia Shows Diverging Microglial State Enrichment



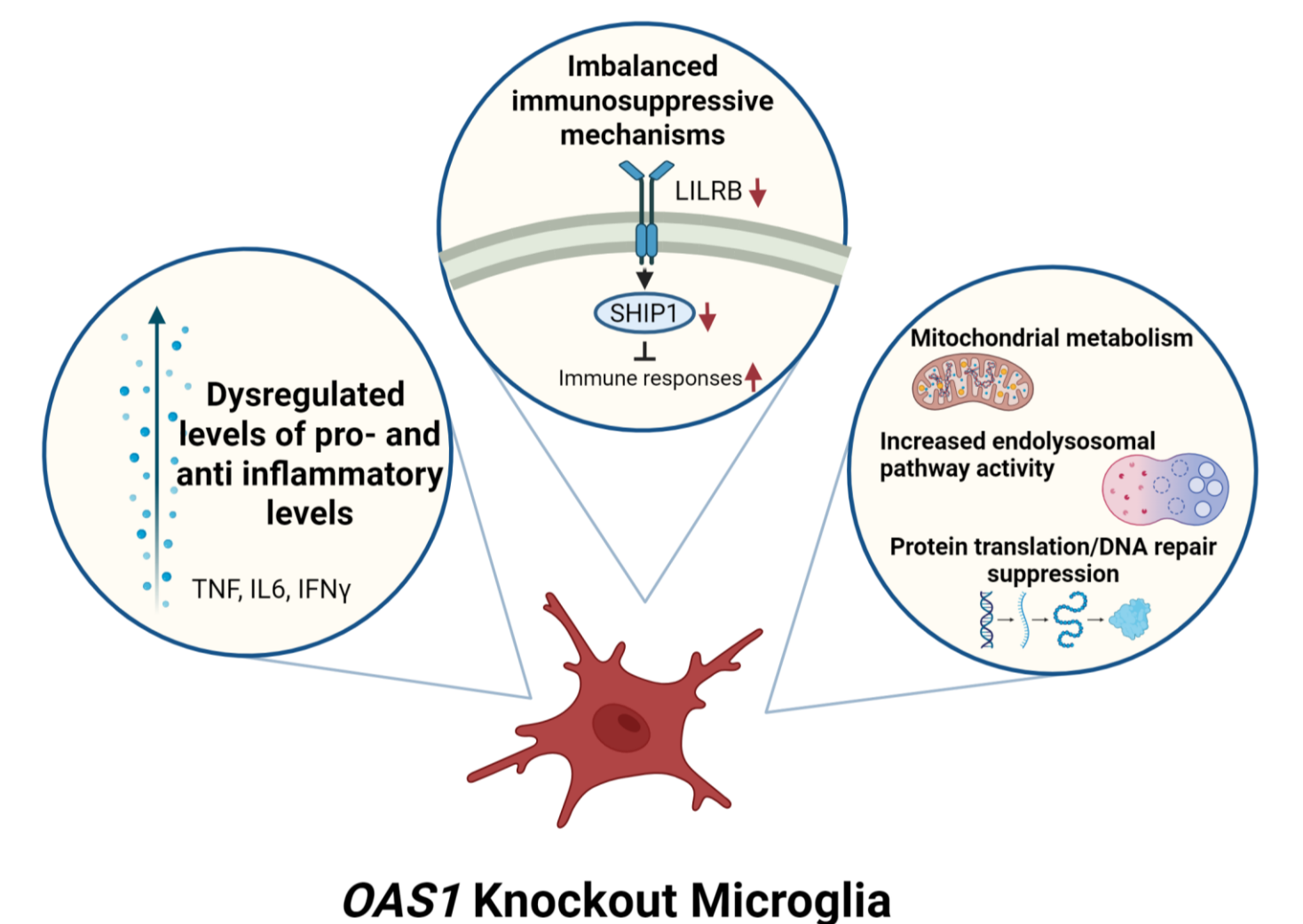
OAS1 KO microglia shows a shift towards **border-associated macrophage (BAM)** phenotype, together with loss of **homeostatic, translational** and **proliferative** states

Identifying the Niche of Interferon-Responsive Cells Using Spatial Transcriptomics (MerScope) in Human AD brain Sections



CONCLUSION

Loss of OAS1 shifts iPSC-microglia away from homeostasis and toward a **state of dysregulated inflammatory, translational, and metabolic balance**, potentially contributing to disease pathology



REFERENCES

- ¹Roy et al., 2020
- ²Sanford et al., 2023
- ³Salih et al., 2019
- ⁴Magusali et al., 2021
- ⁵Lee et al., 2023

CONTACT

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