phosphorylation of RIG-I and MDA5 to a similar extent as PPP1R12C, suggesting PPP1R12C supports the dephosphorylation of RLRS. In agreement with this, depletion of PPP1R12C impaired IFN-β induction in cells stimulated with synthetic dsRNA or infected with SARS-CoV-2, Zika virus or vesicular stomatitis virus (VSV). Similar findings of impaired IFN-β induction and antiviral gene expression were seen in PPP1R12C knockout cells, and in response to VSV infection, Ppp1r12c-deficient mice showed impaired innate immune responses, enhanced viral replication and higher mortality.

Further experiments showed that infection with various RNA viruses causes PPP1R12C binding to RIG-I and MDA5. PPP1R12C also showed increased P1 binding following virus infection, and the authors found that it recruits PPP1 kinases to the RLRS through the formation of PPP1-PPP1R12C-RLRS complexes. PPP1R12C regulates cytoskeleton dynamics as part of the myosin phosphatase complex; therefore, the authors hypothesized that actin cytoskeleton disturbance may displace PPP1R12C from F-actin to promote PP1-PPP1R12C-RLRS complex formation. They confirmed this idea using both viral and non-infectious triggers of cytoskeleton disturbance. Notably, the authors found that full activation of RLRS requires both RNA binding and actin cytoskeleton disturbance. They showed that inducible expression of immunostimulatory RNA in cells only led to antiviral gene expression if cells were also treated with agents that disturb the cytoskeleton and cause relocalization of PPP1R12C.

These findings challenge the current view that the presence of immunostimulatory RNA is sufficient for RLR activation. Instead, the authors propose that full RLR activation requires two key trigger steps: first, actin cytoskeleton disturbance to prime RLRS via PP1-PPP1R12C-RLRS complex formation, and second the detection of immunostimulatory RNA.

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**RESEARCH HIGHLIGHTS**

**IN BRIEF**

**IMMUNOTHERAPY**

**Boosting cytotoxic T cells for immunotherapy**

Two papers in Nature provide insights into the synergistic activity of PD-1-targeted checkpoint inhibitors and IL-2 or IL-2 receptor (IL-2R) agonists. In a mouse model of LCMV infection, Hashimoto et al. show that the binding of IL-2 to CD25 (the IL-2Rα chain) tweak the differentiation programme of antigen-experienced PD-1+ T cells. In contrast, PD-1 inhibition alone, which expands a population of transitory effector T cells that eventually become exhausted, PD-1 blockade combined with IL-2R signalling results in transcriptionally and epigenetically distinct T cells with superior antiviral activity. Codarri Deak et al. achieved similar effects with PD-1-IL2v, which combines PD-1 blockade with an agonist to IL-2Rγ. This molecule enables highly specific targeting of antigen-experienced PD-1+ T cells and avoids CD25-mediated side effects, such as the preferential activation of regulatory T cells and lung endothelial cells. PD-1-IL2v showed promising activity in preclinical cancer models, including a model of pancreatic cancer.

**ORIGINAl ARTICLE** Hashimoto, M. et al. PD-1 combination therapy with IL-2 modifies CD8+ T cell exhaustion program. Nature https://doi.org/10.1038/s41586-022-05157-0 (2022); Codarri Deak, L. et al. PD-1-IL-2R agonism yields better effectors from stem-like CD8+ T cells. Nature https://doi.org/10.1038/s41586-022-05192-0 (2022)

**NEUROIMMUNOLOGY**

**Effect of prenatal stress on the developing brain**

Maternal environmental factors such as poor nutrition, immune activation and aberrant microbiome can affect the prenatal brain. Hayes et al. now investigate how the environment affects the microglia that infiltrate the neuroepithelium in early embryonic development. In a mouse model of maternal immune activation (MIA), the authors show that inflammatory stress leads to the long-term blunting of microglia immune reactivity in the adult offspring, with microglia showing changes in chromatin structure, transcription factor occupancy and transcriptional regulation. They also detected dysfunctional connectivity of the ventral striatal circuit in MIA-exposed offspring, but this could be averted by prenatal replacement of microglia with a physiological infiltration of naive microglia. Thus, prenatal stress can affect neuronal network formation via microglia.

**ORIGINAl ARTICLE** Hayes, L. N. et al. Prenatal immune stress blunts microglia reactivity, impairing neurocircuitry. Nature https://doi.org/10.1038/s41586-022-05127-z (2022)