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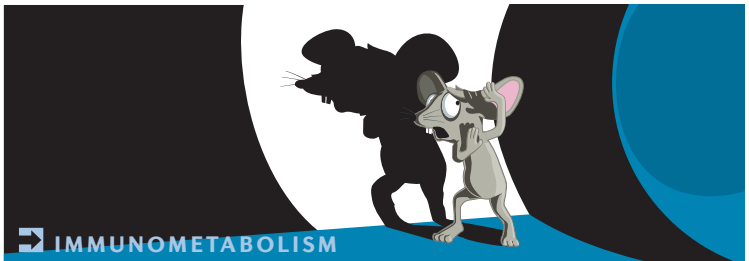

T cells activate the fear

> anti-PD1 therapy administered to tumour bearing mice was also associated with a decrease in serum amino acid concentration

Upon activation, T cells undergo a metabolic shift; naive T cells mainly generate energy through oxidative phosphorylation whereas activated T cells use aerobic glycolysis. The consequences of this shift and the systemic effect of sustained T cell activation are unknown. Now, Miyajima and colleagues report in *Nature Immunology* that an activated T cell phenotype is associated with a depletion of amino acids and neurotransmitters and results in behavioural changes.

The authors carried out metabolomic profiling of serum from *Pdcd1*$^{-/-}$ mice, which are deficient for the inhibitory receptor programmed cell death protein 1 (PD1) and accumulate activated T cells over time. Compared with wild-type controls, 2-month-old *Pdcd1*$^{-/-}$ mice had a substantially decreased abundance of various compounds involved in energy production, including most of the essential amino acids. Importantly, *Cd3e*$^{-/-}$ mice (which lack T cells) had a similar serum amino acid profile to *Pdcd1*$^{-/-}$*Cd3e*$^{-/-}$ mice, suggesting that the *Pdcd1*$^{-/-}$ phenotype was T cell dependent. Furthermore, lymph node-derived activated (CD44^{hi}) T cells from *Pdcd1*$^{-/-}$ mice, and anti-CD3, anti-CD28 stimulated lymph node-derived T cells from wild-type or *Pdcd1*$^{-/-}$ mice had an increased intracellular abundance of tryptophan (Trp) and tyrosine (Tyr) and upregulated expression of amino acid transporters. Targeted metabolome analysis of lymph node tissue from PD1-deficient mice showed differences in the metabolic profile, with a twofold greater abundance of Trp compared with wild type. These data suggest that amino acids accumulate in activated T cells in the lymph nodes and that this causes the depletion phenotype seen in *Pdcd1*$^{-/-}$ mice.

Acute T cell activation that was induced by immunization with ovalbumin was accompanied by a considerable drop in the serum concentration of both Trp and Tyr. In addition, anti-PD1 therapy administered to tumour-bearing mice was also associated with a decrease in serum amino acid concentration. These results further confirm that the phenotype seen in *Pdcd1*$^{-/-}$ mice was associated with T cell activation

Trp and Tyr are essential precursors for the synthesis of the neurotransmitters dopamine and 5-hydroxytryptamine (5-HT, also known as serotonin). These neurotransmitters are thought to regulate various behavioural aspects, including anxiety and fear. Mass spectrometry and liquid chromatography techniques showed that the concentration of Trp, Tyr, dopamine and 5-HT were lower in brain tissue of *Pdcd1*$^{-/-}$ mice than in wild type. Lowered neurotransmitter concentrations seem to translate into altered behaviour, as *Pdcd1*$^{-/-}$ mice showed hypo-locomotion, anxiety-like behaviour and enhanced fear responses in elevated maze, open field and fear conditioning tests. Remarkably, the behaviour of *Pdcd1*$^{-/-}$ mice could be 'rescued' to become similar to the behaviour of wild-type mice by treatment with the selective serotonin reuptake inhibitor fluoxetine or the monoamine-oxidase inhibitor phenelzine, or by dietary supplementation with Trp.

In summary, this study suggests that T cell activation causes a systemic metabolomic shift, which is associated with changes to behaviour. This may have implications for anti-PD1 therapies that are used for cancer immunotherapies in humans.

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ORIGINAL ARTICLE Miyajima, M., *et al.* Metabolic shift induced by systemic activation of T cells in PD-1 deficient mice perturbs brain monoamines and emotional behaviour. *Nat Immunol* http://dx.doi.org/10.1038/ni.3867 (2017)