

## Pregnancy promotes tolerance to future offspring by programming selective dysfunction in long-lived maternal T cells

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### Abstract

Fetal antigen available during pregnancy induces the proliferation of maternal T cells. It is unknown, however, whether these antigen-activated T cells differentiate into long-lived memory T cells that are capable of mediating rapid-recall responses to tissue antigens. To test the hypothesis that pregnancy induces an alternative fate in fetal-specific maternal T cells, we used a murine model to track longitudinally fetal-specific T cells in pregnant and postpartum animals and test the response of these cells when challenged with the same antigen during sequential pregnancy or skin transplantation. Fetal-specific CD8<sup>+</sup> T cells were robustly primed during pregnancy but failed to acquire robust effector functions. These primed cells persisted long term in postpartum animals, frequently maintained a programmed death 1 (PD-1)<sup>+</sup> phenotype, and failed to expand or produce cytokines robustly in response to second pregnancy or skin transplantation. However, whereas there was no impact on second pregnancy as a result of the persistence of fetal-primed memory CD8<sup>+</sup> T cells in the mother, skin grafts bearing the same antigen were rejected more rapidly. Altogether, our data suggest that fetal antigen exposure during pregnancy induces the differentiation of long-lived maternal CD8<sup>+</sup> T cells with context-dependent, selective effector dysfunction. This programmed effector dysfunction provides temporal and systemic restraint of maternal anti-fetal alloreactivity to promote reproductive fitness efficiently, while preserving potentially protective effector T cell responses.

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#### Number of times cited: 5

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