TOLERANCE

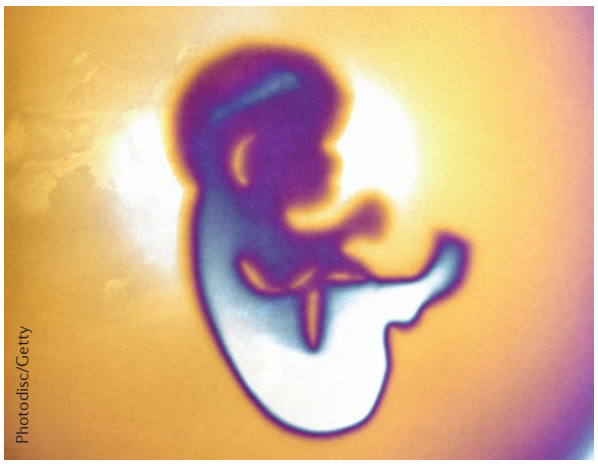
Induced T_{Reg} cells evolved to protect the fetus

Regulatory T (T_{Reg}) cells, the development of which depends on the transcription factor FOXP3, have an essential role in maintaining immune homeostasis. $FOXP3^+$ T_{Reg} cells can develop in the thymus and can also be generated extrathymically (referred to as induced T_{Reg} cells). An emerging concept is that these two populations have distinct functions — that is, thymic T_{Reg} cells mediate tolerance to self antigens, whereas induced T_{Reg} cells control responses to non-self antigens, such as those from food and the commensal microbiota. Reporting in *Cell*, Rudensky and colleagues provide evidence to suggest that induced T_{Reg} cells first emerged in eutherian mammals to reinforce fetomaternal tolerance.

Previous work from this laboratory has described an intronic *Foxp3* enhancer, termed conserved non-coding sequence 1 (CNS1), that is required for the development of induced T_{Reg} cells but is dispensable for that of thymic T_{Reg} cells. Samstein *et al.* examined the conservation of the *Foxp3* CNS1 element in various vertebrate species and found that CNS1 is highly conserved throughout eutherian mammals but is absent from non-eutherian mammals and non-mammals. This indicates that CNS1 emerged in eutherian mammals and suggests a role for induced T_{Reg} cells in protecting fetuses from attack by T cells specific for paternal alloantigens (a process termed fetomaternal tolerance).

To examine this hypothesis in detail, the authors developed a model in which T_{Reg} cells specific for paternal alloantigens could be identified in the decidua during pregnancy. Alloantigen-specific $FOXP3^+$ T_{Reg} cells were detected in the draining lymph nodes and the decidua of female mice following mating with allogeneic but not syngeneic males. The development of these cells was shown to be CNS1 dependent. Furthermore, the rate of embryo resorption was increased in mice lacking CNS1, and these animals had a marked reduction in induced T_{Reg} cell numbers in the decidua compared with controls. The increase was seen in both the percentage of females with resorption and the percentage of resorbed embryos per female, but only in females that mated with allogeneic males and not in those that mated with syngeneic males.

> “a possible link between defective fetomaternal tolerance in humans and impaired induced T_{Reg} cell development or function”



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To confirm a specific role for induced T_{Reg} cells in preventing the ‘rejection’ of MHC-mismatched fetuses, the acute depletion of essentially all T_{Reg} cells in the mouse resulted in a comparable increase in embryo resorption to that observed when only induced T_{Reg} cells were deleted (through CNS1 deficiency). Of note, the decreased percentage of induced T_{Reg} cells in the decidua of CNS1-deficient mice inversely correlated with an increase in activated effector $CD62L^{low}CD4^+$ T cells. Furthermore, T cells were more numerous within all layers of CNS1-deficient placentas, and they clustered in the decidua near spiral arteries.

Finally, the histological features of embryo resorption in mice lacking induced T_{Reg} cells were reminiscent of the abnormal spiral artery remodelling that is associated with pre-eclampsia and other complications of pregnancy in humans, suggesting a possible link between defective fetomaternal tolerance in humans and impaired induced T_{Reg} cell development or function.

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ORIGINAL RESEARCH PAPER Samstein, R. M. *et al.* Extrathymic generation of regulatory T cells in placental mammals mitigates maternal-fetal conflict. *Cell* **150**, 29–38 (2012)