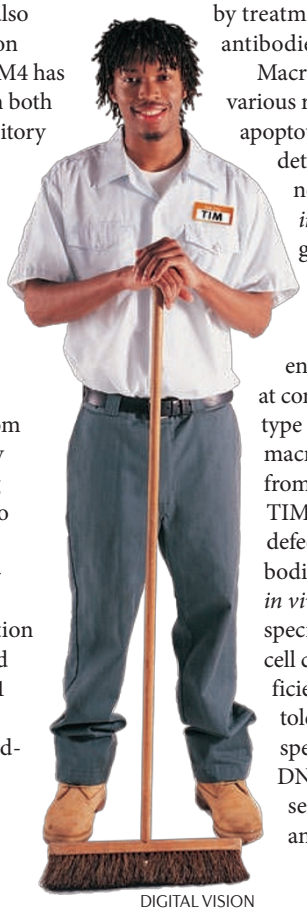
IMMUNE REGULATION

Tidy TIM

The T cell immunoglobulin domain and mucin domain family member TIM4 (also known as TIMD4) is expressed by macrophages and dendritic cells (DCs) and binds to both phosphatidylserine on apoptotic cells and to TIM1 (also known as TIMD1) on activated T cells. TIM4 has been attributed with both activating and inhibitory immune functions but its predominant role *in vivo* has remained unclear. Kuchroo and co-workers have now shown that TIM4 is important for the clearance of apoptotic bodies from the peritoneal cavity and for maintaining immune tolerance to self antigens.

In initial experiments the authors found that, in addition to macrophages and DCs, peritoneal B-1 B cells also express TIM4. Previous studies had shown that treating peritoneal macrophages with TIM4-specific blocking antibodies could prevent their uptake of apoptotic cells. Similarly, the authors found that peritoneal B-1 B cells could engulf apoptotic cells *in vitro* and that this process was inhibited by treatment with TIM4-specific antibodies.



DIGITAL VISION

Macrophages and DCs use various receptors to recognize apoptotic cells; therefore, to determine if TIM4 had a non-redundant function *in≈vivo*, the authors generated TIM4-deficient mice. Splenic macrophages and DCs from TIM4-deficient mice engulfed apoptotic cells at comparable rates to wild-type counterparts. However, macrophages and B-1 B cells from the peritoneum of TIM4-deficient mice showed defective uptake of apoptotic bodies both *in vitro* and *in vivo*. This compartment-specific defect in apoptotic cell clearance seemed sufficient to break peripheral tolerance, as antibodies specific for double-stranded DNA were detected in the serum of TIM4-deficient animals, but not in the serum of wild-type controls. TIM4-deficient mice were found to display other signs of a hyperactive immune system; naive TIM4-deficient mice had increased levels of total serum antibodies, and cells from the draining lymph nodes of TIM4-deficient animals that had been immunized with peptide and adjuvant showed increased proliferation and inflammatory cytokine production following restimulation *in vitro*.

These findings show that TIM4 is important for the uptake of apoptotic bodies by peritoneal macrophages and B-1 B cells, but it is not essential for the clearance of apoptotic bodies in the spleen. However, this compartment-specific defect in TIM4-deficient mice is sufficient to break tolerance to nuclear antigens. Interestingly, the human TIM family gene locus is linked to susceptibility to several autoimmune diseases; this study therefore suggests a mechanism by which defects in TIM4 function might promote the development of autoimmunity.

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ORIGINAL RESEARCH PAPER Rodriguez-Manzanet, R. *et al.* T and B cell hyperactivity and autoimmunity associated with niche-specific defects in apoptotic body clearance in TIM-4-deficient mice. *Proc. Natl Acad. Sci. USA* 5 Apr 2010 (doi:10.1073/pnas.0910359107)