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CELL DEATH

Tumour suppressor p53 helps phagocytes clean up

The tumour suppressor p53 is often referred to as the 'guardian of the genome' as it maintains genomic stability by activating DNA-repair responses and initiating apoptosis in damaged host cells. Now, Yoon *et al.* have found that p53 also promotes the safe removal of apoptotic cells by the immune system by upregulating the expression of an immunoglobulin superfamily receptor death domain 1α (DD1α, also known as platelet receptor Gi24) on dying cells.

> "p53 also promotes the safe removal of apoptotic cells by the immune system"

Using a p53 overexpression system, the author identified *DD1A* as a downstream target of p53 and showed that the expression of DD1α was increased in a p53-dependent manner in cells exposed to genotoxic stressors. However, depletion of *DD1A* using short hairpin RNAs (shRNA) did not affect DNA damage-induced apoptosis in various cell systems, suggesting that *DD1A* may function in a distinct way from typical p53 target genes. As DD1α is structurally similar to members of the T cell immunoglobulin and mucin domain (TIM) family, which have important roles in mediating the phagocytosis of apoptotic cells, the authors examined whether DD1α might have similar functions. Indeed, they found that human monocyte-derived macrophages were less efficient in engulfing apoptotic cells from an MCF7 breast cancer cell-line if *DD1A* or *TP53* (which encodes p53) were depleted from the target cells by shRNA. Similar results were obtained using other cell systems, suggesting that p53-induced expression of DD1α promotes the clearance of apoptotic cells by phagocytes.

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The authors next turned to mouse models to explore DD1α activity *in vivo*. They generated DD1α-deficient mice and exposed these animals to ionizing radiation to induce apoptosis. Compared with wild-type controls, DD1α-deficient animals showed impaired clearance of apoptotic cells in the thymus, lymph nodes and colon. Experiments using DD1α-deficient mouse macrophages indicated that expression of DD1α by both apoptotic cells and macrophages is required for the uptake of apoptotic cells. However, DD1α-mediated clearance of apoptotic cells did not require the expression of phosphatidylserine, which is exposed on the surface of dying cells and is directly recognized by an array of phagocytic receptors. Instead, the authors found that homophilic DD1α interactions are involved in the engulfment of apoptotic cells.

Although the DD1α-deficient mice were born at the expected Mendelian frequency and resembled wild-type littermates early in their life, from the age of 7 to 10 months the majority of female DD1α-deficient animals developed severe skin inflammation and had increased serum levels of anti-nuclear antibodies. By 10 months of age, DD1α-deficient mice had developed glomerulonephritis, splenomegaly and lymphadenopathy and had extensive inflammatory infiltrates in the skin and lungs. Therefore, similarly to mice deficient in various scavenger receptors, mice lacking DD1α develop spontaneous autoimmunity.

DD1α has previously been shown to serve as a negative regulator of T cell activation, and the authors showed that homophilic interactions between DD1α-expressing T cells and DD1α-expressing antigen-presenting cells are important for this role of DD1α. Interestingly, the authors found that in addition to upregulating DD1α, p53 induces the expression of PDL1 and PD1, which are also negative regulators of T cell activation.

In summary, this study identifies a previously unappreciated role for p53 in regulating the immune system, both by promoting the clearance of apoptotic cells and by upregulating the expression of negative regulators of T cell activation. Interestingly, the authors propose that the activation of p53 in tumour cells in response to genotoxic stress may result in the upregulation of immune checkpoint molecules that actually limit anti-tumour T cell responses.

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ORIGINAL RESEARCH PAPER Yoon, K. W. *et al.* Control of signaling-mediated clearance of apoptotic cells by tumor suppressor p53. *Science* http://dx.doi.org/10.1126/science.1261669 (2015)