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Meeting abstract

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Gadd45β-induced prolonged activation of p38 kinase defines a novel pathway mediating negative selection of thymocytes

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The clonal deletion of thymocytes by negative selection is an important process to ensure immunologic tolerance, even though the underlying molecular mechanisms are poorly understood. Here, we show that Gadd45β, a regulator of mitogen-activated protein kinases, is critically involved in triggering negative selection. Gadd45β expression was inducible in different models of negative selection. Strikingly, only TCR-ligating peptides resulting in negative selection, but not positively selecting ligands or dexamethasone, a TCR-independent apoptosis agonist, induced Gadd45β expression. Expression of Gadd45β maintained a sustained activation of p38 kinase and thereby promoted TCR-mediated apoptosis. In contrast, inhibition of Gadd45β expression or p38 activity impaired cell death. Moreover, thymocytes from Gadd45β-deficient mice revealed only transient p38 activation, reduced caspase activation and cell death. Thus, we provide evidence that Gadd45β and a resulting persistent activation of p38 constitute a novel apoptotic pathway involved in negative selection.