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Meeting abstract

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An atypical NF-kappa B-regulated pathway mediates phorbol ester-dependent Heme oxygenase-1 gene activation in monocytes

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Heme oxygenase (HO)-1 is the rate-limiting enzyme of heme degradation. More recently, HO-1 has been shown to have anti-inflammatory and antioxidant functions, which have been demonstrated in HO-1 knockout mice models and a human case of HO-1 genetic deficiency. Moreover, targeted induction of HO-1 has been shown to have therapeutic effects in various disease models. Here, it is reported that the HO-1 gene is transcriptionally induced by the phorbol ester phorbol myristate acetate (PMA), which is a prototypical activator of PKC, in various monocytic cells. The PMA-dependent induction of HO-1 has a different time-dependent pattern of induction from that of lipopolysaccharide-dependent HO-1 induction in these cells. Activation of HO-1 by PMA was mediated via a newly identified kB element of the proximal rat HO-1 gene promoter region (-284 to -275). This HO-kB element was a nuclear target for the NF-kB subunit p65/RelA as determined by nuclear binding assays and transfection experiments with luciferase reporter gene constructs in RAW264.7 monocytes. Moreover, PMA-dependent induction of endogenous HO-1 gene expression and promoter activity was abrogated in embryonic fibroblasts from p65-/- mice. PMA-dependent HO-1 gene activation was reduced by an overexpressed dominant negative mutant of IkB, but not by dominant negative IkB kinase-2 (IKK2) suggesting that the classical NF-kB pathway was not involved in this regulation. The antioxidant N-acetylcysteine and inhibitors of p38 MAPK or serine/threonine kinase CK2 blocked PMA-dependent HO-1 gene activation. Finally, it is demonstrated by luciferase assays with a Gal4-CHOP fusion protein that activation of p38 MAPK by PMA was independent of CK2. Taken together, induction of HO-1 gene expression by PMA is regulated via an IKK-independent atypical NF-kB pathway that is mediated via activation of p38 MAPK and CK2.