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Regulation of Nur77 Expression by Activation of T Cell Receptor

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TCR-mediated apoptosis in immature T cell has been important for eliminating self-antigen reactive T cells and Nur77 has been identified to be a crucial gene for TCR-mediated thymocyte apoptosis. Nur77 (NGFI-B/TR3) is an NR4A1-3 subgroup of orphan nuclear receptors (Nur77, NOR-1, Nurr1) and mediates apoptotic pathways in prostate cancer cells, lung cancer cells, gastric cancer cells as well as immature T cell.

Recently the molecular mechanism by which TCR-mediated calcium signal induces Nur77 in T cell has been explosively elucidated. Myocyte enhancing factor 2 (MEF2) has been highlighted as a calcium-dependent transcription factor that regulates gene expression of muscle, neuron, and immune cells. MEF2D, a predominant isoform in T cell, is found to bind to two calcium-dependent DNA elements in the Nur77 promoter and to mediate calcium-dependent induction of Nur77. It has been so far known that two distinct calcium-mediated pathways are involved in the regulation of MEF2 transcription activity: (i) Calcium-sensitive corepressors of MEF2; transcription factors are generally regulated by histone acetylation and deacetylation, which is mediated by two opposite types of enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs). Coactivators (p300/CBP, SRC1/2) directly bind to transcription factor and catalyze histone acetylation with intrinsic HAT domain, whereas HDACs repress the transcriptional activity through indirect binding of cognate repressor-mSin3-HDAC complex or direct binding to transcription factor. Three distinct types of cognate repressors for MEF2 have been identified, Cabin1/Cain, HDAC4, 5, 7, 9 and MITR. All of them were revealed to have ability of recruiting HDACs. These HDAC-repressors dissociate with MEF2 by competition with calmodulin for binding to MADS box of MEF2 transcription factor in a calcium dependent manner. Moreover, the activities of calmodulin-dependent kinase (CaMK) I and IV interrupt the interaction between MEF2 and HDAC4/5 and cause the nuclear export of HDAC4/5 (McKinsey et al., 2000). (ii) Binding of calcineurin-activated NF-AT to MEF2D; NF-AT, a well-known calcineurin substrate, binds to MEF2 on the Nur77 promoter in a DNA-binding element independent manner, implicating that NF-AT acts as a coactivator of MEF2D transcription factor for Nur77 induction .

In spite of main role of calcium signal in TCR-mediated Nur77 induction, it is important to recall that TCR-activated protein kinase C (PKC) also functions as a regulator in the life and death of T cell. PKC family of serine/threonine kinases are thought to play roles in a variety of cellular functions in different types of tissues. Among these, PKCθ is expressed predominantly in skeletal

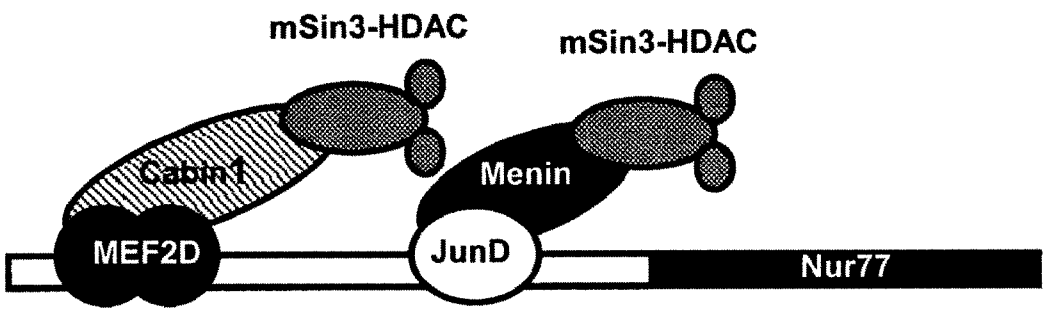
muscle and lymphoid organs. PKCθ has been known to participate in the regulation of interleukin-2 in T lymphocytes by the mechanism of selective stimulation of AP-1 transcription factor, synergistic activation of JNK with calcineurin, and the activation of NF-kB through selective activation of IkB kinaseβ. (IKKβ) by CD3-CD28 costimulation.

Menin is a tumor suppressor protein encoded by MEN1 (multiple endocrine neoplasia type I), a causative gene related with tumors of parathyroid, enteropancreatic neuroendocrine tissue and anterior pituitary. Menin is a 610-amino-acid nuclear protein, and specifically interacts with JunD but not with other members of Jun family (c-Jun, JunB) because their interactions are mediated through the far N-terminal region of JunD lacking in c-Jun and JunB. Moreover, Menin are known to interact with other transcription factors, NF-kB, Smad3, and Pem, implicating that Menin is deeply related with transcriptional activity. Menin is known to repress JunD-activated transcription, however, detailed molecular mechanism by which menin represses JunD is still unclear. Gobl and his colleagues recently showed that HDAC inhibitor, trichostatinA re-augments Menin-repressed JunD transcriptional activity, suggesting that HDAC-related repressors may be involved in the Menin-JunD repression.

In this study, we demonstrated that PKCθ activates JunD transcriptional activity through MAP kinase-mediated phosphorylation and cooperation of JunD with p300 acetyltransferase in Nur77-mediated T cell apoptosis. Moreover, we elucidated that Menin is involved in repression of JunD transcriptional activity through recruitment of mSin3-histone deacetylase complexes. Taken together with our previous result that calcium regulates MEF2 transcriptional activity by controlling association of MEF2 with Cabin1-HDAC complexes and p300 acetyltransferase during Nur77-mediated apoptosis in T cell apoptosis (Youn et al., 1999; Youn and Liu, 2000; Youn et al., 2000a), we, herein, suggest another regulatory mechanism by which PKCθ synergizes Nur77 expression in T cell by controlling association of JunD with Menin-HDAC complexes and p300 acetyltransferase.

A proposed mechanism by which TCR regulates Nur77 expression

A. Quiescent Cell



B. TCR-Activated Cell