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NFκB- and AP-1-mediated DNA looping regulates matrix metalloproteinase-9 transcription in TNF-α-treated human leukemia U937 cells

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ABSTRACT

The aim of this study is to explore the spatial association of critical genomic elements in the effect of TNF-α on matrix metalloproteinase-9 (MMP-9) expression in human leukemia U937 cells. TNF-α up-regulated MMP-9 protein expression and mRNA level in U937 cells, and Akt-mediated-NFκB/p65 activation and JNK-mediated c-Jun activation were proven to be involved in TNF-α-induced MMP-9 up-regulation. Promoter luciferase activity assay revealed that NFκB (nt-600) and AP-1 (nt-79) binding sites were crucial for TNF-α-induced transcription of MMP-9 gene. The results of a chromatin immunoprecipitation assay indicated that TNF-α reduced histone deacetylase-1 (HDAC-1) recruitment but increased p300 (a histone acetyltransferase) recruitment to MMP-9 promoter regions surrounding NFκB and AP-1 binding sites. Consistently, TNF-α increased enrichment of the acetylated histone H3 mark on MMP-9 promoter regions. DNA affinity purification assay revealed that p300 and HDAC1 could bind oligonucleotides containing AP-1/c-Jun and NFκB/p65 binding sites. Chromosome conformation capture assay showed that TNF-α stimulated chromosomal loops in the MMP-9 promoter via NFκB/p65 and AP-1/c-Jun. The p300-associated acetyltransferase activity was crucial for p65/c-Jun-mediated DNA looping, and inhibition of HDAC activity increased the level of DNA looping. Reduction in the level of DNA looping eliminated all TNF-α-stimulated MMP-9 up-regulation. Taken together, our data suggest that p65/c-Jun-mediated DNA looping is involved in TNF-α-induced MMP-9 up-regulation and that the recruitment of p300 or HDAC1 to NFκB and AP-1 binding sites modifies the level of DNA looping.

1. Introduction

Tumor necrosis factor-α (TNF-α) is implicated in inflammation-associated cancers produced either by tumor cells alone or by tumor cells and infiltrating leukocytes [1]. TNF-α biological functions are mediated through its receptors, TNFR1 and TNFR2 [2]. Nevertheless, TNF-α relies largely on TNFR1 for apoptosis induction and gene transcription activation. An interesting feature of TNF-α signaling is the existence of crosstalk between the pro-apoptotic and NFκB-activating pathways [3]. TNF-α-elicited NFκB activation has been demonstrated to be related to cancer cell survival, metastasis, and progression [4–6].

Multiple lines of evidence suggest that matrix metalloproteinases (MMPs) promote tumor progression. The MMP-mediated degradation of the extracellular matrix contributes to promote angiogenesis, tumor growth, and metastasis [7]. MMP-2 and MMP-9 are presumed to be especially important for cell transmigration since these proteinases act on type IV collagen and other basement membrane components [8]. In leukemia, excessive egress of leukemic blast cells from the bone marrow into the peripheral blood can cause invasion of the leukemic blast cells into various organs and tissues [9,10]. MMP-2 expression plays a role in the development of increased vessel density observed in the bone marrow of patients with acute myeloid leukemia by facilitating in vitro endothelial cell migration [11]. Moreover, cell surface association between MMP-2/-9 and integrins has been suggested to be involved in the growth and progression of acute myeloid leukemia and chronic myeloid leukemia cells [12]. Several lines of evidence indicate a role for MMP-9 in the pathogenesis of acute and chronic myeloid leukemias [13–17]. Some studies show that TNF-α induces MMP-9 expression or secretion in leukemia cells [18–20]. Moreover, the TNF-α-mediated signaling pathway has been found to contribute to acute myeloid leukemia progression [21]. Thus, understanding the events responsible for TNF-α-induced MMP-9 expression will facilitate the development of promising new strategies for suppressing invasion/migration of leukemia cells.

Several studies reveal that epigenetic mechanisms, including histone acetylation, histone methylation, DNA methylation and non-coding RNAs, are crucially involved in MMP-9 expression [22,23]. Other studies show that TNF-α-induced MMP-9 expression is associated with histone

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