ERK2-mediated C-terminal serine phosphorylation of p300 is vital to the regulation of epidermal growth factor-induced keratin 16 gene expression.

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Keratins, which are the most prominent cytoskeletal proteins in keratinocytes, belong to a large family of about 30 epithelially specific intermediate filament proteins that form the cytoskeleton (1). Among these, keratin 16 is usually referred to as an activation- and hyperproliferation-associated keratin because it is reported to be the marker in the hyperproliferated skin diseases including psoriasis (2, 3). A recent study indicates that keratin 16 is induced in human papilloma virus-infected tissues at the transcriptional level, and more importantly, the induction leads to the proliferation of keratinocytes, a known characteristic of human papilloma virus infection (4). Therefore, a full understanding of the gene regulation of keratin 16 might contribute to therapies beneficial to those hyperproliferated diseases. We have previously proposed a model for the transcriptional regulation of keratin 16 (5, 6). We suggest that the epidermal growth factor (EGF) up-regulates the recruitment of coactivator p300 to the promoter of keratin 16 through the activation of ERK, the last being of critical importance for the EGF regulation of keratin 16. We also show that the recruited p300 functionally cooperates with Sp1 and c-Jun to enhance the gene expression of keratin 16. Therefore, the aim of this work was to study how the ERK activation regulated the recruitment of p300, thereby activating the keratin 16 gene expression.

In human keratinocytes HaCaT cells, EGF apparently induced time- and dose-dependent phosphorylation of p300, both in vitro and in vivo, through the activation of ERK2. The six potential ERK2 phosphorylation sites, including three threonine and three serine residues as revealed by sequential analysis, were first identified in vitro. Confirmation of these six sites in vivo indicated that these three serine residues (Ser-2279, Ser-2315, and Ser-2366) on the C terminus of p300 were the major signaling targets of EGF. Furthermore, the C-terminal serine phosphorylation of p300 stimulated its histone acetyltransferase activity and enhanced its interaction with Sp1. These serine phosphorylation sites on p300 controlled the p300 recruitment to the keratin 16 promoter. When all three serine residues on p300 were replaced by alanine, EGF could no longer induce the gene expression of keratin 16. In...
summary of this study (7), as shown in Figure 1, C-terminal serine (Ser-2279, Ser-2315, and Ser-2366) phosphorylation sites on p300 were the major targets by ERK2 activation upon EGF treatment, leading its recruitment to the keratin 16 promoter. Once recruited, phosphorylated p300 might enhance its interaction with Sp1 as well as acetylate histone H3 on the keratin 16 promoter via its increased histone acetyltransferase HAT activity. As a consequence, p300 enhanced EGF-induced gene expression of keratin 16.

Our findings provided a better understanding between the activity of p300 and disease-associated keratin 16 overexpression. As mentioned above, keratin 16 is usually referred to as an activation- and hyperproliferation-associated keratin specifically reported to be the marker in the hyperproliferated skin diseases, such as psoriasis (2, 3). Psoriasis is a common inflammatory skin disorder that affects about 0.1–3% of the world’s population (8). Although psoriasis does not ordinarily affect the general health of a patient, the unsightliness can be detrimental, although sometimes underestimated, to the social and psychological welfare of a patient. However, the understanding of its pathogenesis is still limited. Analysis of the transcriptional regulation of the psoriasis-associated keratin 16 gene will provide important insights into the pathogenesis of psoriasis and may thus help to improve treatments by providing novel therapies in the future.

References:


