shown, DHEAS did not show synergy with ATRA during NB4 differentiation, suggesting that DHEA acts as a ligand of a nuclear receptor. Because a synergistic effect of DHEA and ATRA was detected only when ATRA was used at a low concentration, the downstream signaling of DHEA may converge to ATRA signaling and thus amplify the final common pathway of NB4 cell differentiation. That DHEA alone had no effects on NB4 cell differentiation indicates that a low dose of ATRA is required, not only for the differentiation trigger but also for an elicitation of DHEA's actions. ATRA possibly induces the expression of a still-unknown DHEA receptor.

Even at a low concentration, ATRA induced the histone H3 acetylation of the $p67^{phox}$ gene, and this mechanism may be responsible for the observed enhanced transcription of this gene by ATRA (Figure 4). DHEA alone, however, did not induce histone H3 acetylation of $p67^{phox}$ and had no enhancing effect on ATRA-induced histone H3 acetylation, in spite of its enhancing effect on the transcription of $p67^{phox}$ in the presence of ATRA. Thus, DHEA conceivably affected $p67^{phox}$ transcription via a mechanism independent of histone H3 acetylation. Several possible mechanisms could explain these phenomena. For example, DHEA might directly activate the transcription factors for the $p67^{phox}$ gene, such as Sp1, PU.1, AP-1, and C/EBPβ [24]. Alternatively, DHEA might stabilize $p67^{phox}$ messenger RNA, resulting in its accumulation.

There are no major qualitative differences in the actions of ATRA and DHEA, both of which have been hypothesized to use nuclear receptors to initiate the transcription of target genes during cellular differentiation. In contrast, DHEA did not induce histone H3 acetylation of the $p67^{phox}$ gene under the conditions of ATRA-induced $p67^{phox}$ gene acetylation. Thus, the 2 agonists seem to act on cells via similar but not identical pathways. Similar parts of the signaling pathways cross-talk with each other, and an independent pathway may induce additive or synergistic effects. Further study is required for a comprehensive understanding of the complex cross-talk between ATRA and DHEA. In particular, identification of a possible nuclear receptor for DHEA is the most important problem to be resolved.

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