**Mechanism of cAMP-PKA regulation of estrogen-dependent transcription in breast cancer.**

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The majorities of breast cancers express estrogen receptor-alpha (ERα) and thus are estrogen-dependent. This makes the ERα a specific molecular target that can be efficiently inhibited by drugs. Unfortunately, in a significant percentage of patients, the treatment fails because of acquiring drugs resistance. Therefore, the mechanisms of ERα pathway drug resistance and the means of circumventing them represent high-priority fields in breast cancer research. The molecular mechanism and the steps required for transcription initiation induced by nuclear hormones are still unknown, although several protein-DNA complexes enucleated by nuclear hormone receptors have been extensively characterized (<doi>:10.1016/j.cels.2017.08.011; 10.1101/gad.552910). For example, in the case of estrogens, it has been shown that the receptor (ERα) recruits to the Estrogen Responsive Elements (EREs) the co-activator complex that modifies the chromatin and drive the assembly of the initiation complex.

We have specifically addressed the mechanism(s) by which the Co-activator complex induces the transcription of E2-sensitive genes. We have found that the demethylating enzyme LSD1 (KDM1A), a flavin adenine dinucleotide-dependent amine oxidase, is essential for E2-transcription initiation. LSD1 catalyzes the demethylation of mono or di-methylated histone H3 lysine 4 (H3K4, open chromatin) and lysine 9 (H3K9, closed chromatin). This demethylation generates a wave of DNA oxidation necessary for the formation of transcription loops joining the ERE-the transcription start site(s) and the 3’ end of the gene(s) (doi: 10.1038/s41598-019-40123-6). Here we demonstrate that the cAMP-dependent protein kinase A (PKA) phosphorylates threonine 110 in LSD1 and favors the interaction of the enzyme with the initiation transcription complex. In particular, we show that E2 -PKA axis induces the interaction between LSD1, the N-terminal domain of ER-α, and the large subunit of RNA polymerase II. In fact, the treatment with specific inhibitor(s) of estrogen receptor binding and/or PKA reduces significantly the formation of the complex ER-α - RNA polymerase II subunit. PKA phosphorylates threonine 110 *in vitro* and stimulates the formation of the complex E2-R and RNA polymerase II subunit. The expression of the LSD1 mutant (Threo to Ala) decreases the formation of the complex of RNA polymerase II with receptor, although is the receptor is recruited to the ERE upon E2 induction, but does not stimulate E2-induced transcription. In conclusion, these findings explain the cAMP-PKA potentiating effects on E2 biological action(s) and identify possible targets to inhibit the E2 biological response (doi: 10.1038/sj.onc.1210027; 10.3390/ijms21186490).