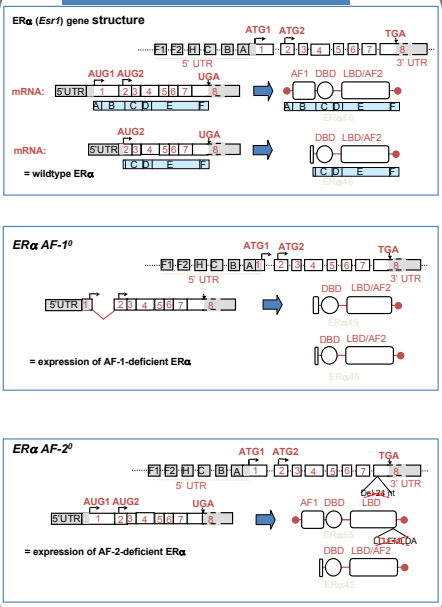
THE TRANSACTIVATING FUNCTION-1 OF ESTROGEN RECEPTOR ALPHA IS DISPENSABLE IN THE VASCULOPROTECTIVE ACTIONS OF 17β-ESTRADIOL

Aim of the project

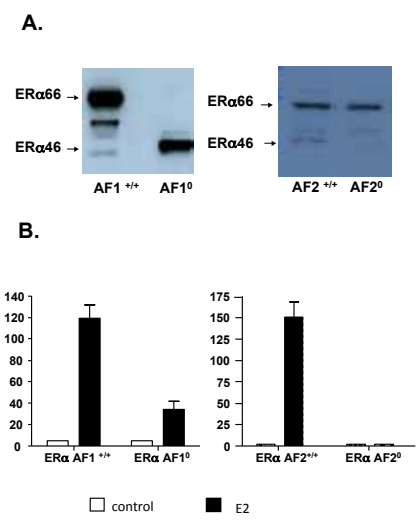
Full length 66kDa estrogen receptor alpha (ERα) stimulates target gene transcription through two activation functions (AF), AF-1 in the N-terminal domain and AF-2 in the ligand binding domain. Another physiologically expressed 46kDa ERα isoform lacks the N-terminal A/B domains and is consequently devoid of AF-1. The aim of the present work was to directly evaluate the involvement of ERα AF-1 and ERα AF-2 in two major vasculoprotective effects of E2, i.e the reendothelialization process and the development of atherosclerosis. To this end, we developed mouse model, the first lacking the ERα A/B domains that we named *ERαAF-1⁰* and the second in which amino acid 543 to 548 of ERα were deleted, that we named *ERαAF-2⁰*

Generation of ERα AF-1⁰ and AF-2⁰ mice



Schematic representation of the wildtype ERα gene *(Esr1)* and the targeted AF1⁰ and AF2⁰ function.

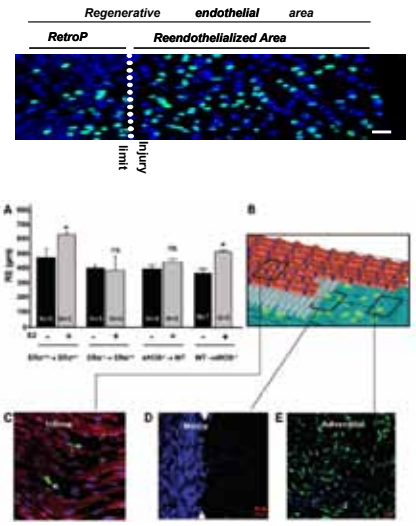
ERα AF-1 and AF-2 are necessary for the E2 uterotrophic action



A. ERα protein level were assessed by western blot analysis of 15µg protein from ERα AF1+/+, ERα AF1⁰, ERα AF2+/+, ERα AF2⁰

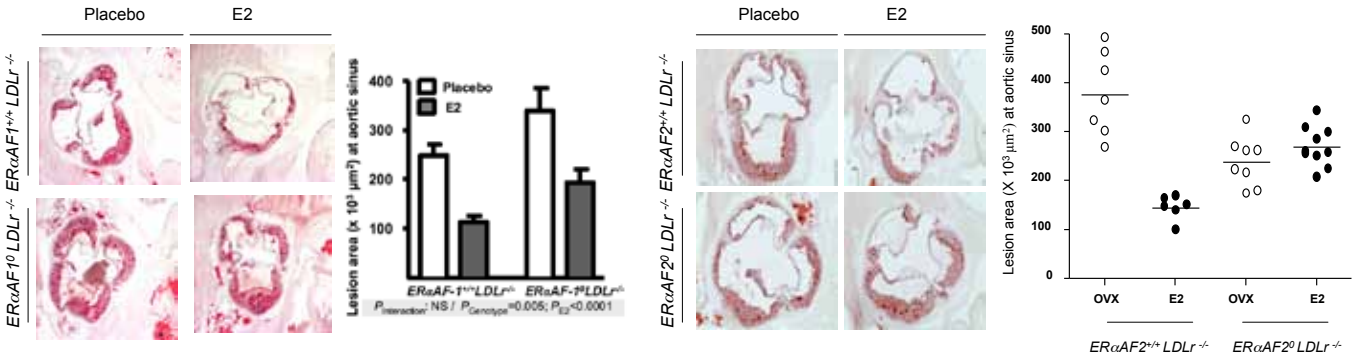
B. Uterine weight from mice treated or not with E2 (80µg/kg/day).

ERα AF-1 and AF-2 are dispensable for the effect of E2 on carotid endothelial healing



En face confocal microscopy

Whereas ERα AF-1 is dispensable, ERα AF-2 is necessary for the E2 atheroprotective effect



Exogenous E2 prevents fatty streak deposit in 18-week-old ERαAF-1⁰ and ERαAF-2⁰ mice
Four-week-old ovariectomized mice were given either placebo or E2 (80µg/kg/day during 12 weeks) and switched to atherogenic diet from the age of 6 to 18 weeks.
Representative micrographs of Oil red-O lipid stained cryosections of the aortic sinus. Scale bars correspond to 200 µm and quantification (mean ± SEM) of lesion area at the aortic sinus from an average of 7 or 8 mice per group.

Conclusion

In these *ERαAF-10* mice, both basal endothelial NO production and reendothelialization process were increased by E2 administration in a similar extent than in control mice. Furthermore, exogenous E2 similarly decreased fatty streak deposits at the aortic root from both ovariectomized 18 week-old *ERαAF-1+/+ LDL-r-/-* (Low Density Lipoprotein receptor) and *ERαAF-10 LDL-r-/-* mice fed with a hypercholesterolemic diet. In addition, quantification of lesion size on *en face* preparations of the aortic tree of 8 month-old ovariectomized or intact female mice revealed that ERα AF-1 is dispensable for the atheroprotective action of endogenous estrogens. We conclude that ERα AF-1 is not required for three major vasculoprotective actions of E2, whereas it is necessary for the effects of E2 on its reproductive targets. Thus, Selective Estrogen Receptor Modulators stimulating ERα with minimal activation of ERα AF-1 could retain beneficial vascular actions, while minimizing the sexual effects.

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PUBLICATIONS

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