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# Inclusion of 17?-estradiol into liposome: a new tool to study the molecular mechanisms of estrogen receptors

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Estrogens are implicated in many physiological and pathological processes thanks to their interaction with estrogen receptors (ERs). The estrogen receptor alpha (ER?) controls reproduction and mammary gland development. Its contribution to breast cancer progression and prognosis is also well established. The molecular mechanisms sustaining these biological processes are extremely complex and remain an area of intense academic research. The activation of ER? by estrogens and especially by 17?-estradiol (E2) leads to 2 major pathways: (1) the genomic effects associated to the transcriptional activity of the ER? and (2) the MISS (Membrane Initiated Steroid Signaling) effects related to the induction of fast signaling pathways occurring when ER? is anchored to the plasma membrane.

In order to better understand the respective impact of these two ER-associated signaling pathways on physiopathology, new specific tools are mandatory. The aim of this work was to validate if the inclusion of E2 into liposome was able to prevent the activation of the MISS pathway, while remaining efficient to induce the genomic pathway.

The formulation of E2 encapsulated into liposome (named POPC E2) was tested in vitro and in vivo in paradigms specifically described to be dependent on the genomic pathway or on the MISS pathway. To study the genomic pathway, the expression of two target genes of this pathway, PR and pS2, was studied by RT-qPCR in MCF7 cells. POPC E2 increased the mRNA expression level of PR and pS2, highlighting its ability to induce ER?-genomic pathways. In addition, POPC E2 was able to increase the uterine impregnation, the wet weight, the percentage of Ki67-positives cells and the epithelial height, similarly to E2. The activation of the MISS pathway was studied in a Proximity Ligation Assay (PLA) experiment measuring the interaction between ER? and Src, the initiating step of the MISS effects. POPC E2 did not induce any increase of ER?-Src interaction. The expression of target genes of the MISS pathway (TSKU, HSPB8, PMAIP1) revealed no induction by POPC E2.

In conclusion, POPC E2 promotes the ER?-associated genomic pathways and prevents the activation of the MISS pathway. Our results highlight that the inclusion of E2 into liposome is an interesting tool to delineate the complex molecular mechanisms associated to ER activation.

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