The nuclear localization signal is required for nuclear GPER translocation and function in breast Cancer-Associated Fibroblasts (CAFs).

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ABSTRACT Cancer associated fibroblasts (CAFs) actively contribute to the growth and invasion of cancer cells. In recent years, the G protein estrogen receptor (GPER) has been largely involved in the estrogenic signals in diverse types of normal and tumor cells. In CAFs, GPER was localized into the nucleus, however the molecular mechanisms which regulate its nuclear shuttle remain to be clarified. In the present study, we demonstrate that in breast CAFs GPER translocates into the nucleus through an importin-dependent mechanism. Moreover, we show that a nuclear localization signal is involved in the nuclear import of GPER, in the up-regulation of its target genes c-fos and CTGF and in the migration of CAFs induced by estrogens. Our data provide novel insights into the nuclear localization and function of GPER in CAFs toward a better understanding of the estrogen action elicited through these key players of the tumor microenvironment.