

L. Chellini¹, V. Caprara¹, F. Spadaro², R. Sestito¹, A. Bagnato¹ and L. Rosanò¹

¹Preclinical Models and New Therapeutic Agent Unit, IRCCS-Regina Elena National Cancer Institute, Rome, Italy

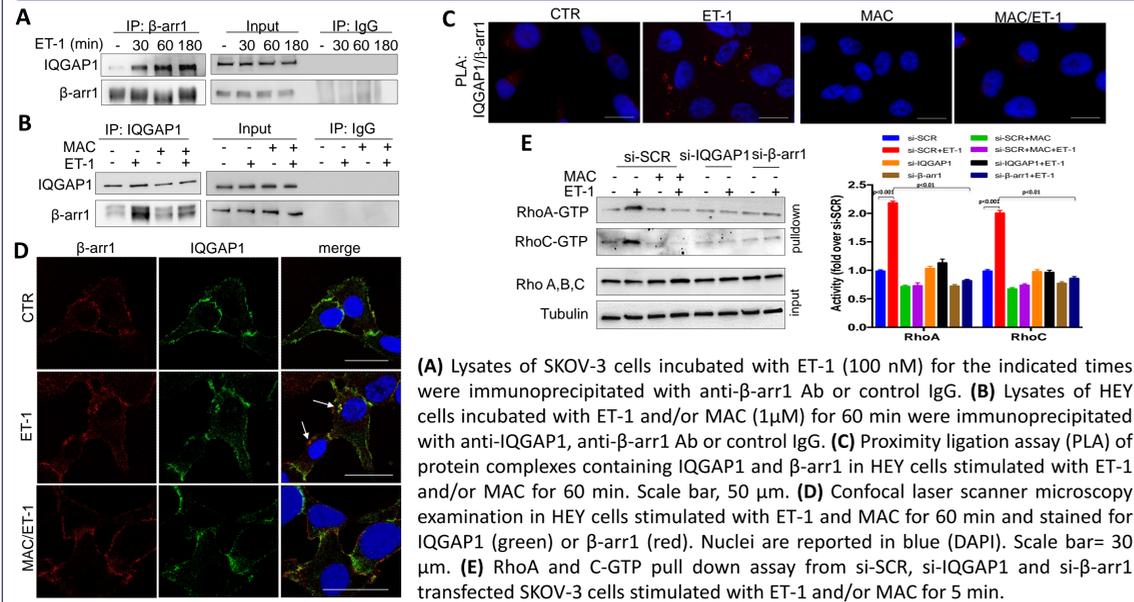
²Confocal Microscopy Unit, Istituto Superiore di Sanità, Rome, Italy

BACKGROUND

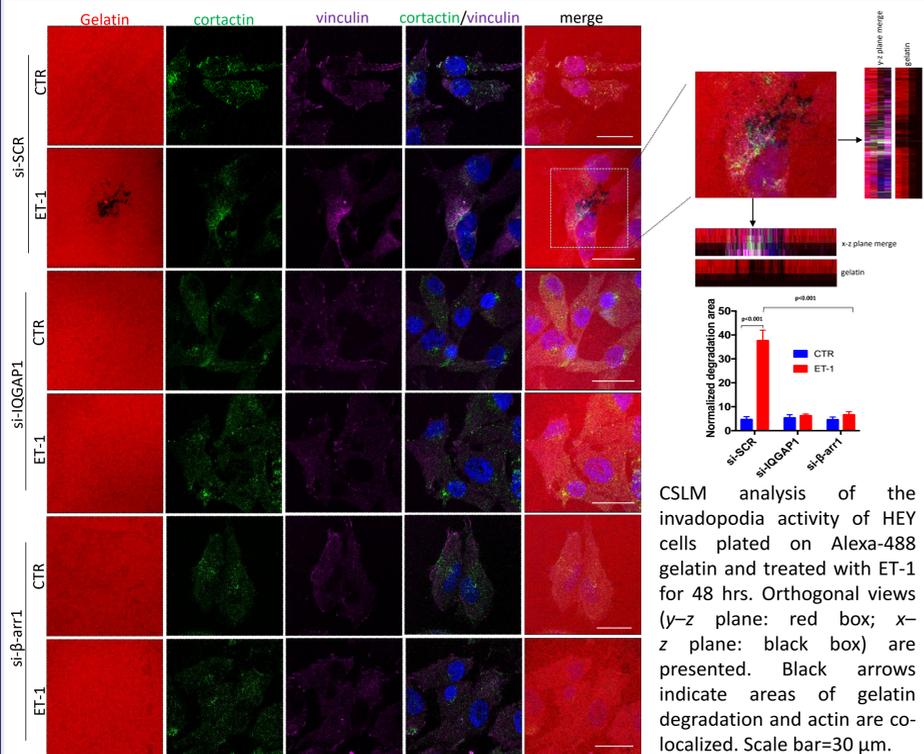
- To metastasize, tumor cells must be able to degrade and remodel the extracellular matrix and the underlying vasculature, which can be accomplished through activity of invadopodia, actin-rich adhesive membrane protrusions with a complex molecular structures, hotspots for secretion of matrix-degrading metalloproteinases (MMPs).
- The endothelin-1 receptor (ET-1R) has a critical role in ovarian cancer (SOC) progression, by controlling different tumor promoting effects, including invasion and metastasis, which are mediated by β -arrestin1 (β -arr1), acting as molecular hub that orchestrates active signaling complexes.
- We recently reported that upon ET-1R activation, β -arr1 regulates actin regulators to form invadopodia.

The aim of this study is to investigate whether ET-1R/ β -arr1 axis might operate through a cross-talk with invadopodia regulators, such as IQGAP1, to promote invadopodia assembly.

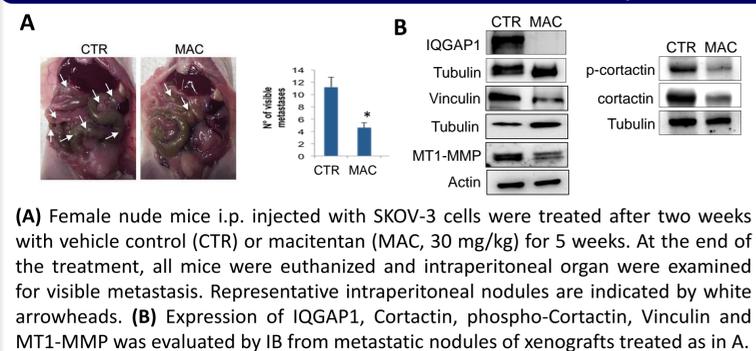
2. ET-1R activation promotes association of IQGAP1 with β -arr1 to activate Rho A/C GTPases



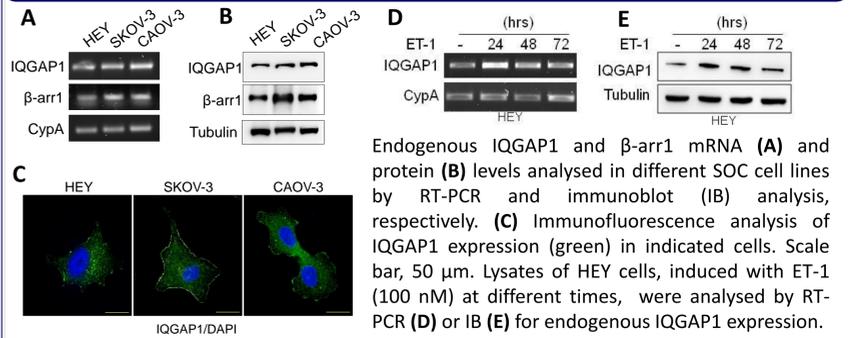
4. IQGAP1 is required in ET-1R-induced invadopodia activity



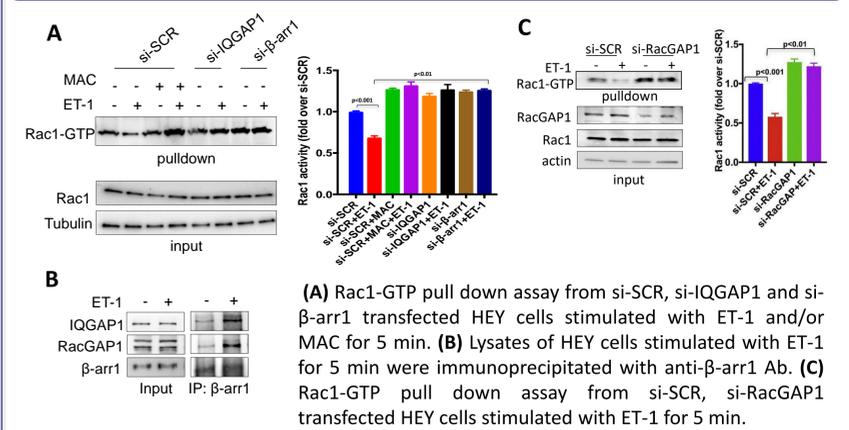
6. ET-1 receptor blockade impairs metastatic behaviour and interferes with IQGAP1 expression



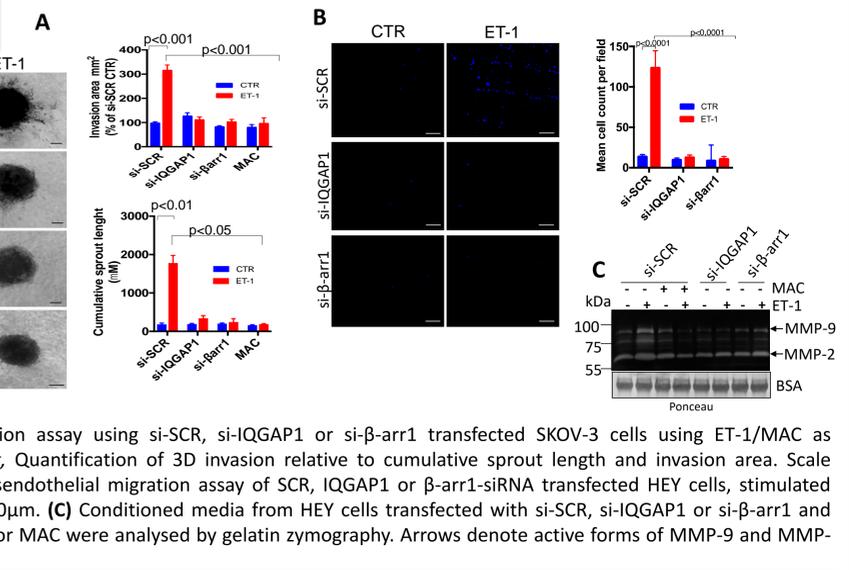
1. ET-1 regulates IQGAP1 in SOC cells



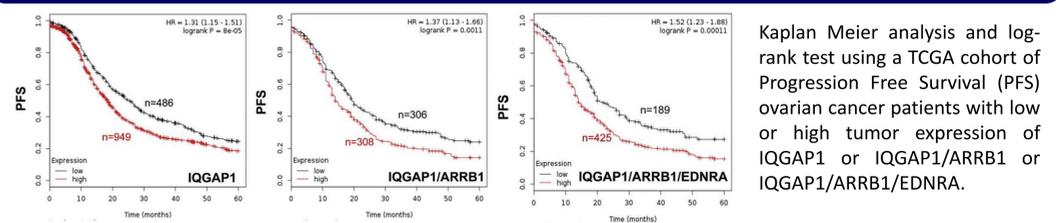
3. ET-1R/ β -arr1 network promotes Rac1 deactivation through RacGAP1



5. IQGAP1/ β -arr1 network is required in the ET-1R-induced MMP activation and cell invasion



7. IQGAP1/ARRB1/EDNRA expression as prognostic gene signature in HG-SOC patients



Conclusions

- Engagement of IQGAP1 by ET-1R/ β -arr1 favours invadopodia function and aggressive behaviour of SOC cells.
- Interruption of ET-1R/IQGAP1/ β -arr1 network impairs invadopodial function and metastatic behaviour of SOC cells, indicating the therapeutic efficacy of MAC.
- High expression level of EDNRA/IQGAP1/ β -arr1 correlates with poor prognosis suggesting a clinical implication of these factors in SOC progression.

