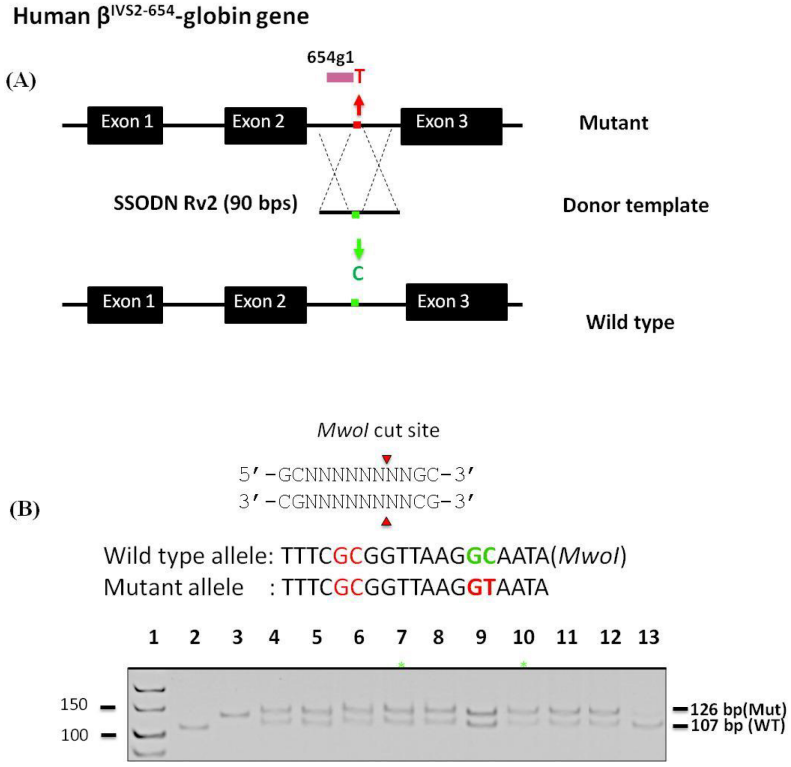
Figure 3



References

1. Xu P, Tong Y, Liu X-z, et al. Both TALENs and CRISPR/Cas9 directly target the HBB IVS2–654 (C > T) mutation in β-thalassemia-derived iPSCs. Sci Rep. 2015/07/09 2015;5(1):12065. https://doi.org/10.1038/srep12065

2. Liang X, Potter J, Kumar S, Ravinder N, Chesnut JD. Enhanced CRISPR/Cas9-mediated precise genome editing by improved design and delivery of gRNA, Cas9 nuclease, and donor DNA. J Biotechnol. 2017;241:136-146. https://doi.org/10.1016/j.jbiotec.2016.11.011

3. Liu Y, Yang Y, Kang X, et al. One-Step Biallelic and Scarless Correction of a β-Thalassemia Mutation in Patient-Specific iPSCs without Drug Selection. Mol Ther Nucleic Acids. 2017;6:57-67. https://doi.org/10.1016/j.omtn.2016.11.010

P0967 | Discovery, molecular modeling and biological evaluation of 1,3,5-triaril-pyrazole derivatives as novel Estrogen Receptor Modulators

Priscila López-Rojas[2]; Ángel Amesty[2]; Yeray Fernández-Sánchez[1]; Miguel Guerra-Rodríguez[1]; Sergio Santana-Viera[1]; Carlota Recio[1]; Borja Guerra[1]; Ana Estévez-Braun[2]; Leandro Fernández-Pérez[1]

[1]University of Las Palmas de Gran Canaria – IUIBS; [2]University of La Laguna - IUBO

Introduction

The biological actions of estrogens are mediated by estrogen binding to one of two specific estrogen receptors (ERs), ERα and ERβ. The ERs, which belong to the nuclear receptor superfamily of ligand-regulated transcription factors, are products of different genes and exhibit tissue- and cell-type specific expression. Clinically relevant, ERs are currently considered relevant drug targets for prevention and/or treatment of several diseases (from cancer, metabolic and cardiovascular, inflammation, and osteoporosis to neurodegeneration). In this work, new derivatives of 1,3,5-triaril-pyrazoles were designed, synthesized and evaluated in vitro as Estrogen Receptor Modulators.

Method

Virtual screening and Fluorescent Polarization assay together with real-time microphotography cell proliferation analysis and ER-based drug discovery strategies (1) were used to evaluate a chemical library enriched in ERα-based 1,3,5-triaril-pyrazoles derivatives.

Results

In this work, we found that certain substituted pyrazoles are high-affinity ligands for the hERα and hERβ (from 40 to 200 nM). The results obtained in the binding assay with hREα correlate with the obtained in the in silico studies, confirming that the presence of hydroxyl groups on

aromatic rings B and C in the structure of 1,3,5-triaryl pyrazole derivatives is critical for a favorable interaction with ERα. They can also activate ERα-dependent transcription in adenocarcinoma breast cancer cells with high potency (EC50 < 1μM) but with a relative efficacy lower (50-80%) than pure agonist E2. They also promote cell proliferation of ER+ breast cancer cells with EC50 below 5 μM. However, antiestrogenic activity of E2-induced breast cancer cell proliferation was observed in the presence of 1,3,5-triaril-pyrazoles derivative concentration above 5 μM.

Conclusions

In this study, we have identify novel 1,3,5-triaril-pyrazoles derivatives as pure agonists of ER and, other ones, with partial agonist/antagonist activity on ERα-mediated transcription and proliferation of human ER+ breast adenocarcinoma cells.

Reference

1. Guerra-Rodríguez M et al. Discovery of Highly Functionalized 5-hydroxy-2H-pyrrol-2-ones That Exhibit Antiestrogenic Effects in Breast and Endometrial Cancer Cells and Potentiate the Antitumoral Effect of Tamoxifen. Cancers 2022, 14(21):5174.

P0969 | Confirmation of Proposed Xenohormetic Protection by Phytochemicals in Human Microphysiological Models of Tissue Vasculogenesis and Cancer-Induced Angiogenesis

Kevin Conrad[1]; Gideon Wills[1]; Ethan Byrne[1]; Matthew Burow[2]; Mark Mondrinos[1]
[1]Department of Biomedical Engineering, Tulane University; [2]Tulane Cancer Center, Dept. of Medicine, Tulane University School of Medicine

Introduction/Background & aims

Citrus flavonoids such as Naringenin present in grapefruit exert anti-stress effects in the plants and phytoalexins such as Glyceollin present in soybean are involved in the plant defense against infection. Understanding these effects in the context of human tissue and organ models is a necessary step in defining the health-promoting effects of diets enriched with specific micronutrients and improving the accuracy of decisions to scale up commercial production of candidate phytochemicals to accelerate preclinical research and eventual translation. We utilized microphysiological assays of 3D tissue vasculogenesis and cancer-induced angiogenesis engineered in our laboratory to test the inhibitory effects of phytochemicals from a USDA panel on multiple morphogenetic processes relevant to tumor vascularization.

Method/Summary of work

HLF and HUVEC were incorporated in hydrogels composed of collagen type I and fibrin to create stromal vascular tissues. We engineered a PDMS device for culturing an array of disc-shaped tissue constructs to test the dose-dependent effects of Naringenin (grapefruit flavonoid), it's derivative Sakuranetin, and Glyceollin (soybean phytoalexin) on vasculogenesis. We performed morphometric analysis of 3D confocal image data to quantify the structural features of emergent vascular networks in the tissues. Membrane-free organ chips that enable patterning of adjacent but contiguous layers of tissues with defined compositions were loaded with the same cell-hydrogel mixture used for tissue vasculogenesis in one lane, and hydrogel containing spheroids derived from the biopsy of a patient with highly aggressive triple negative breast cancer in the adjacent lane. We quantified phytochemical effects on vascular morphometry and sprouting in the cancer-containing tissue space.

Results/Discussion

A tissue array assay allowed rapid screening of phytochemical dose responses (Fig. 1A). Naringenin (NAR) potently inhibited de novo vasculogenesis in stromal vascular tissues at and above 25 uM (Fig. 1A). Sakuranetin (SAK) only partially inhibited vasculogenesis at 125 uM, despite being a metabolic derivative of NAR. Glyceollin (GLY) inhibited vasculogenesis, though to a lesser degree than NAR at the same doses. We used the minimal effective dose of 25 uM identified in vasculogenesis studies to test phytochemical inhibition of cancer-induced angiogenic processes and found that NAR completely inhibits vascularization, whereas SAK has no effect (Fig. 1C).

Conclusion(s)

Our study provides quantitative evidence of potent anti-vasculogenic, and anti-angiogenic effects elicited by USDA-specified candidate phytochemicals in multiple human cell-based MPS models. Therefore, we conclude that further investigation of phytochemicals as potential therapeutic agent in MPS models of human cancers is warranted.