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Study the effect of cycloporin a on functionality of endothelial cells differentiated from induced pluripotent stem cells as in vitro toxicity model

Zahra Mazidi, Matthias Wieser, Regina Grillari-Voglauer and Johannes Grillari

Evercyte GmbH, Austria

Abstract

Backgrounds and Objectives: Designing a suitable in vitro model of vascular system could lead us understanding the mechanism which chemicals affecting them. Due to 3R principles, we are trying for alternative models to animal testing. Stem cells specially induced pluripotent stem cells (iPSCs) with ability of differentiation to all organs of body including vascular system could be a good substitute. In this study we differentiated iPS cells toward endothelial cells using a novel cocktail of small molecules and growth factors as a model for our toxicology assessment. We started our toxicity part using cyclosporin A(CSA) which is known as a potent immunosuppressive agent in pharmacologic studies. Beside the positive effect of CSA, there is emerging evidence showing its effect on inducing long-term vascular dysfunction and angiogenesis impairment in patients. We designed this study in order to get deeper insights into effect of CSA on angiogenesis of endothelial cells and finding out the exact mechanisms.

Materials and Methods: iPS cells were derived from two normal donors fully characterized and after proving their pluripotency characteristics were treated with a cocktail of growth factors and small molecules for differentiation to endothelial cells. QPCR, Flow cytometry and immunostaining analysis demonstrated high yield of differentiation. In the next step we checked the effect of CSA on endothelial cells viability through resazurin assay. To understand CSA effect on endothelial cells functionality we modified sprouting assay method which measures the angiogenesis process. The progress of CSA toxicity was also tracked through mitochondrial changes and ATP assay.

Results: Endothelial cells differentiated from iPS cells expressed CD31 and VE-Cadherin as endothelial cells markers and showed functional characteristics using matrigel assay. CSA showed EC50 around 5µM on endothelial cells viability. Mitochondrial experiments proved a deficiency in mitochondrial complexes of endothelial cells after CSA treatment. Also CSA treatment could increase ATP synthase in our cells which altogether leaded to impaired angiogenesis checked by sprouting assay.

Discussion and Conclusion: So by now, we could design an in vitro model of endothelial cells help us finding out exact toxicity of CSA on endothelial cells focusing on angiogenesis impairment in patients.

Biography

Zahra Mazidi is and Iranian student, studying her PhD in Evercyte GmbH, a Biotechnology based company focused on Acceleration of drug finding and development as an Early Stage Researcher involved in IN3 Innovative Training Network program (Marie Skłodowska-Curie Early Stage Researcher - in3). In this role, she started her PhD in combination of stem cell differentiation to vascular system and toxicology field. Her most exciting work might be designing an animal free model for drug screening.

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