
Hypoxia and trophoblast differentiation: a key role for PPARgamma

Journal: Stem Cells Dev

Publication Year: 2013

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PubMed link: 23767827

Funding Grants: Interdisciplinary Stem Cell Training Program at UCSD II

Public Summary:

Tissue oxygen tension regulates differentiation of multiple types of stem cells. In the placenta, hypoxia has been associated with abnormal trophoblast differentiation and placental insufficiency syndromes of preeclampsia (PE) and intrauterine growth restriction (IUGR). Peroxisome proliferator-activated receptor- γ (PPAR γ) is a ligand-activated transcription factor involved in many cellular processes, including differentiation. We have previously shown that PPAR γ -null trophoblast stem (TS) cells show a defect in differentiation to labyrinthine trophoblast, instead differentiating preferentially to trophoblast giant cells (TGC). Since PPAR γ is known to be regulated by hypoxia in adipose tissue, we hypothesized that there may be a link between oxygen tension, PPAR γ expression, and trophoblast differentiation. We found that hypoxia reduced PPAR γ expression by a mechanism independent of both hypoxia-inducible factor (HIF) and histone deacetylases (HDACs). In addition, PPAR γ partially rescued hypoxia-induced inhibition of labyrinthine differentiation in wild-type TS cells but was not required for hypoxia-induced inhibition of TGC differentiation. Finally, we show that induction of labyrinthine trophoblast differentiation by HDAC inhibitor treatment is independent of both PPAR γ and Gcm1. We propose a model with two pathways for labyrinthine trophoblast differentiation of TS cells, one of which is dependent on PPAR γ and inhibited by hypoxia. Since hypoxia is associated with PE and IUGR, we propose that PPAR γ may at least partially mediate hypoxia-induced placental insufficiency and as such may be a promising therapeutic target for these disorders.

Scientific Abstract:

Tissue oxygen tension regulates differentiation of multiple types of stem cells. In the placenta, hypoxia has been associated with abnormal trophoblast differentiation and placental insufficiency syndromes of preeclampsia (PE) and intrauterine growth restriction (IUGR). Peroxisome Proliferator-Activated Receptor-gamma (PPARgamma) is a ligand-activated transcription factor involved in many cellular processes, including differentiation. We have previously shown that PPARgamma-null trophoblast stem (TS) cells show a defect in differentiation to labyrinthine trophoblast, instead differentiating preferentially to trophoblast giant cells (TGC). Since PPARgamma is known to be regulated by hypoxia in adipose tissue, we hypothesized that there may be a link between oxygen tension, PPARgamma expression, and trophoblast differentiation. We found that hypoxia reduced PPARgamma expression by a mechanism independent of both hypoxia-inducible factor (HIF) and histone deacetylases (HDACs). In addition, PPARgamma partially rescued hypoxia-induced inhibition of labyrinthine differentiation in wild-type TS cells but was not required for hypoxia-induced inhibition of TGC differentiation. Finally, we show that induction of labyrinthine trophoblast differentiation by HDAC inhibitor treatment is independent of both PPARgamma and Gcm1. We propose a model with two pathways for labyrinthine trophoblast differentiation of TS cells, one of which is dependent on PPARgamma and inhibited by hypoxia. Since hypoxia is associated with PE and IUGR, we propose that PPARgamma may at least partially mediate hypoxia-induced placental insufficiency and as such may be a promising therapeutic target for these disorders.

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