



# UNIVERSITÀ DEGLI STUDI DI TORINO

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## **Indoleamine-2,3-deoxygenase (IDO1) oxygen-mediated regulation in normal, preeclamptic and chronic kidney disease (CKD) placentae**

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Background: IDO1 is key a heme-enzyme expressed by the human placenta. Through depletion of oxygen and tryptophan and kynurenine production, it reduces proliferation and activity of T cells avoiding maternal-placental “rejection”. Moreover, IDO1 plays a role in reactive oxygen species management and it is inversely correlated to oxidative stress (OxS).

Preeclampsia (PE) is a placenta-related syndrome characterized by abnormal maternal immune-response leading to aberrant placenta development and oxidative stress. According to the maternal/placental immune-maladaptation model, a role for IDO1 in PE pathogenesis has been hypothesized but never accurately demonstrated.

Herein, we characterized IDO1 placental oxygen-mediated regulation and its expression in PE and CKD placentae, clinically indistinguishable from PE despite a different etiology and no placental compromise.

Methods: Human term placental villous explants (n = 21) were cultured for 12h at 20%pO<sub>2</sub>. Next, explants were treated oxygen-filled nanobubbles (OLNs-500 ul) and incubated in hypoxic conditions (3%pO<sub>2</sub>) or standard conditions (20%pO<sub>2</sub>) for 8 h. Untreated explants at 3%/20%pO<sub>2</sub> were used as controls. Physiological (n = 15), PE (n = 15) and CKD (n = 21) placentae were collected. Placental biopsies and explants were processed for mRNA isolation. IDO1 mRNA levels were determined by Real Time PCR.

Results: IDO1 mRNA levels were significantly increased in 20%pO<sub>2</sub>+OLNs (p<0.05, 8.3 Fold Increase; OxS condition) and 3%pO<sub>2</sub> (p<0.05, 4.6 Fold Increase) explants vs 20%pO<sub>2</sub> controls. Interestingly, 3%pO<sub>2</sub>+OLNs explants showed a reduction of IDO1 mRNA levels (p<0.05, 2.0 Fold decrease) vs 3%pO<sub>2</sub> controls. IDO1 expression was significantly reduced in PE compared to both CKD and control placentae (p < 0.05).

Conclusions: In the present study, we demonstrated, for the first time to our knowledge, IDO1 oxygen-mediated expression in the human placenta. IDO1 down-regulation further contributes to the pathological OxS environment typical of PE placentae. CKD placentae showed normal IDO1 expression, underlying a physiological placental environment.

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