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DEFENSE OF THE DOCTORAL

DISSERTATION

“The epithelial-mesenchymal transition in cytotrophoblast differentiation is mediated by the zinc finger E-box binding protein 2 (ZEB2)”

by

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ABSTRACT

The differentiation of trophoblast cells is a vital process required for successful placentation. Proliferative cytotrophoblast (CTB) at the tips of the anchoring cell columns differentiate into invasive extravillous cytotrophoblast (EVT) that invade into the uterus. Various reports describe factors that alter the invasive behavior of trophoblast cells, but limited attention has been given to the mechanisms that form the invasive EVT. The differentiation of the non-motile, epithelial-like CTB into invasive EVT has been described as an epithelial-mesenchymal transition (EMT), similar to that in embryogenesis (a Type 1 EMT), but it also resembles a Type 3 EMT when neoplastic cells acquire metastatic properties. The objectives of this dissertation are to identify the mechanisms underlying normal trophoblast differentiation into EVT, and to investigate these mechanisms in abnormal placental pathologies of under- and over-invasion. To interrogate the mechanism of CTB differentiation, we measured EMT markers in CTB and EVT from normal first- and third-trimester placenta. Our results indicate that as CTB differentiate into EVT, a loss of epithelial markers occurs concomitant with a gain of mesenchymal markers in the first trimester, supporting previous suggestions that CTB/EVT differentiation is an EMT. In the third trimester, the EVT have reverted to a more epithelial phenotype while retaining mesenchymal markers. The zinc-finger E-box binding protein 2 (ZEB2) transcription factor, described in other EMT types, is significantly upregulated during first-trimester but its expression diminishes at term. We show ZEB2 is more highly expressed in abnormally invasive placenta (AIP), an over-invasion pathology, compared to gestational age-matched controls. However, ZEB2 is suppressed in preeclampsia (under-invasive pathology), again compared to gestational age-matched controls. We demonstrate, using a novel 3D-bioprinted placental model in combination with Transwell assays and xCELLigence system, that ZEB2 overexpression in epithelial-like trophoblast cells modifies functionality, causing an increase in invasiveness of these previously anchorage-dependent cells. Taken together, these studies indicate a major role for ZEB2 in trophoblast EMT.

Significance: The studies in this dissertation provide insights into the mechanism by which CTB are transformed into EVT and lay the foundation for more targeted studies of AIP. Our results support the description of trophoblast differentiation as an EMT.