B-Raf and Epigenetic Regulation of Placentation

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Defective placentation has been associated with the “great obstetrical syndromes”. Placentation is a complex process and relies on the coordinated regulation of various pathways. Others and we observed that B-Raf expression increases from 9.5 days post coitum (dpc) to 11.5 dpc during placentation. B-Raf$^{-/-}$ mice are not viable and die at 10.5 to 11.5 dpc. Necropsy demonstrates vascular malformation with thin and dilated fetal vessels with apoptotic cells in mice's placentas with disorganized trophoblast layers. Of note, conditional knockout of B-Raf only in the epiblast (not in trophoblast) did not lead to fetal demise. This evidence supports that placental vascular defect secondary to trophoblast dysregulation in B-Raf$^{-/-}$ mice is the chief cause of mid-gestation fetal death and not vasculature in fetus per se. Thus, we tested the hypothesis that B-Raf kinase regulates trophoblast apoptosis through the B-Raf-STAT-Bcl2 pathway. Results demonstrate that B-Raf- Signal Transducer and Activator of Transcription 3 (STAT3)-Bcl2 is critical for the survival of these cells. Furthermore, B-Raf kinase regulates promoter methylation and histone phosphorylation to mediate downstream effects. The findings indicate that B-Raf epigenetically regulated trophoblasts’ survival and placentation.