Adverse Effects of Nucleotide Excision Repair and Transcription Gene Abnormalities on Human Fetal and Placental Development

A. Kumar[1], A. Dzutsev[2], and R. Moslehi[1*]

[1]School of Public Health, State University of New York (SUNY) at Albany, NY

[2]National Cancer Institute (NCI), NIH, Frederick, MD

* Corresponding Author: Roxana Moslehi, PhD, Assistant Professor, School of Public Health and Cancer Research Center, State University of New York at Albany, NY.

Our recent genetic epidemiologic investigation of gestational outcomes associated with abnormalities in trichothiodystrophy nucleotide excision repair (NER) and transcription genes, namely *XPD*(*ERCC2*), *XPB*(*ERCC3*), *TTD-A*(*GFT2H5*), and *TTDN1*(*C7ORF11*), revealed significantly increased risk of several severe gestational complications including preeclampsia in affected pregnancies where the fetus had two mutations, but not in unaffected pregnancies where the fetus was either heterozygote or had no mutations. To test our hypothesis that DNA repair/transcription genes are involved in normal placental development and decipher biologic mechanisms, we analyzed gene expression arrays of normal human placentas and placentas from pregnancies complicated with preeclampsia. We found high expression of NER/transcription genes in human placenta, above the mean of their expression in all organs. *XPD*, *XPB*, and *TTDN1* were consistently expressed from 14 to 40 weeks gestation while expression of *TTD-A* was strongly-negatively correlated ($r=0.7$, $P<0.0001$) with gestational age. Meta-analysis of case-control studies of preeclampsia containing global gene expression patterns in placentas followed by pathway analysis revealed imbalance of several dominant pathways

including DNA-dependent regulation of transcription and response to oxidative stress pathways, known to be regulated by NER/transcription genes. Our results indicate an important role for NER/transcription gene products during normal human placental development and provide clues as to the etiology of observed gestational complications associated with abnormalities in these genes. Our results implicate dysfunction of DNA-dependent regulation of transcription and response to oxidative stress pathways caused by abnormalities in these genes as relevant mechanisms leading to preeclampsia.