WRIGHT STATE UNIVERSITY | BIOMEDICAL SCIENCES PhD PROGRAM

**Dr. David Ladle, Director**
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# DISSERTATION DEFENSE

## AMJAD ALJAGTHMI
## PhD Candidate

**"The regulation of small GTPase Rac1 phosphorylation, activation and subcellular localization by ΔNp63α."**

**Thursday, July 29th, 2021**

**1:00 p.m.**

**Collaborate Ultra**
https://us.bbcollab.com/guest/b8e290632a624fd0bc01af69c352f19a

***Advisor: Madhavi Kadakia, PhD***
***Associate Dean of Research Boonshoft School of Medicine***
***Interim Vice Provost for Research***

**Aljagthmi, Amjad, Biomedical Sciences PhD Program**
**Wright State University, 2021**

ΔNp63α, a member of the p53 family of transcription factors, is overexpressed in a number of cancers and has been shown to regulate microRNAs involved in cancer cell invasion. Here, we studied the effects of ΔNp63α on Rac1 phosphorylation, activation and localization. We have identified a novel ΔNp63α/miR-320a/PKCγ signaling pathway that regulates Rac1 function via altered phosphorylation. We showed that miR-320a is a direct target and positively regulated by ΔNp63α. We further showed miR-320a targets PKCγ and thereby negatively regulates Rac1 phosphorylation at S71. Increased pRac1 and cell invasion observed upon knockdown of ΔNp63α were reversed by miR-320a mimic overexpression, Rac1 silencing or PKCγ inhibition. *In silico* analysis demonstrated a positive correlation between ΔNp63α and miR-320a in human cervical squamous cell carcinoma (CESCC) and a negative correlation with PKCγ and enhanced long-term survival. We showed that ΔNp63α silencing increased the levels of GTP-Rac1 and its downstream target pPAK1, indicating ΔNp63α negatively regulates Rac1 GTP activation. We demonstrated that Rac specific GEF P-Rex1 is a direct target of ΔNp63α. Further, P-Rex1 knockdown abrogated the increase in GTP-Rac1 levels resulting from ΔNp63α knockdown, but did not rescue pRac1 levels. ΔNp63α knockdown in JHU-006 cells decreased endogenous nuclear Rac1 localization and increased plasma membrane Rac1 and pRac1. Finally, we showed that ΔNp63α and Rac1 directly interact and that this interaction is enhanced via the GTP-binding but is not by phosphorylation. Taken together, our data suggest that ΔNp63α negatively regulates Rac1 phosphorylation and GTP binding, thereby inhibiting cancer cell invasion.