Michael Piacentino
Marianne Bronner Group
Postdoctoral Fellow, Third Year

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**Intracellular attenuation of BMP signaling via CKIP-1/Smurf1 is essential during neural crest induction**

ABSTRACT: The neural crest is a multipotent and migratory cell population that contributes to diverse structures including the peripheral nervous system and the craniofacial skeleton. Neural crest induction occurs at the neural plate border downstream of signaling inputs including FGFs, BMPs, and Wnts. While intermediate BMP levels were proposed as critical for neural crest induction in frog and zebrafish, secreted BMP antagonists appear to be dispensable in chick, raising the question of how the required intermediate BMP levels are generated. Here, we propose a morphogen model where intracellular attenuation of BMP signaling sets the required intermediate levels to maintain neural crest induction. We show that the scaffold protein CKIP-1, and ubiquitin ligase Smurf1, are co-expressed with BMP4 at the chick neural plate border. Knockdown of CKIP-1 during a critical period between gastrulation and neurulation provoked loss of neural crest cells, while Smurf1 knockdown increased neural crest numbers. At a mechanistic level, we find that CKIP-1 and Smurf1 modulate BMP signaling upstream of pSmad1/5/8 accumulation and transcriptional activity, thereby facilitating a dose-dependent response to BMP signals. Through biochemical and epistasis experiments, we discovered that Smurf1 targets receptor Smads for degradation, and CKIP-1 acts to promote Smurf1 autodegradation. Together these results support a model in which CKIP-1 suppresses Smurf1-mediated degradation of Smads, thereby uncovering a novel intracellular mechanism to attenuate BMP signaling to the intermediate levels required to maintain neural crest. Our new model suggests that neural plate border cells “fine-tune” BMP signaling autonomously and reconciles discrepant results on the roles of secreted BMP antagonists from adjacent tissues during neural crest induction. This work was supported by NIH grants F32 HD088022, R01 DE024157 and P01 HD037105.