

P020 Molecular Mechanisms of cAMP-mediated Neural Crest Cell Development

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The neural crest (NC) a pluripotent, embryonic cell population differentiates to diverse cell types including sympathetic neurons, adrenal medullary cells and melanocytes. The intensity of cAMP signaling is a differential instructive signal in neural crest (NC) specification. Moderate cAMP in combination with BMP2 promotes the sympathoadrenal lineage by inducing via CREB, transcription of proneural transcription factor Phox2a. Further, cAMP regulates Phox2a activity by an OA-sensitive dephosphorylation step. cAMP via Phox2a activation induces transcription of cyclin-dependent kinase inhibitor p27^{kip1}, coordinating cell cycle exit and neuronal differentiation.

High level activation of cAMP signaling induces melanogenesis and suppresses sympathoadrenal lineage development via PKA-dependent Rap1-B-Raf-ERK1/2 activation and cytoplasmic translocation of phospho-Smad1. Concurrently, cAMP via CREB induces transcription of melanocyte-determining transcription factor Mitf and melanogenesis. However, constitutively active CREB without PKA activation is insufficient for Mitf expression, indicating PKA regulates additional aspects of Mitf transcription. Our studies demonstrate the transcriptional co-repressor CtBP is regulated by PKA and involved in Mitf transcription and melanogenesis.