Alternative RNA splicing of transcripts encoding protein serine/threonine kinases downstream of PDGFR signaling in the facial mesenchyme

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Craniofacial development is a complex morphogenetic process, disruptions in which result in highly prevalent human birth defects. Signaling through the platelet-derived growth factor receptors (PDGFRs) plays critical roles in this process in humans and mice. However, the gene expression changes that mediate cellular activity downstream of PDGFRalpha and/or PDGFRbeta signaling are incompletely understood. Here, we performed sequencing of maxillary process mesenchyme RNA from E11.5 mouse embryos that lack *Pdgfra*, *Pdgfrb* or both in the neural crest lineage to examine the transcriptional output in each context. DESeq2 analysis identified 23, 20 and 25 genes that were differentially expressed between *Pdgfra*$^{fl/fl}$*;Wnt1-Cre*$^{+/Tg}$, *Pdgfrb*$^{fl/fl}$*;Wnt1-Cre*$^{+/Tg}$ and *Pdgfra*$^{fl/fl}$*;Pdgfrb*$^{fl/fl}$*;Wnt1-Cre*$^{+/Tg}$ samples as compared to wild-type, respectively. In contrast, rMATS analysis detected over 5,000 differential alternative RNA splicing (AS) events per genotype compared to wild-type samples, with the majority of events involving skipped exons. Gene ontology (GO) analysis of the genes encoding the transcripts in the skipped exon category of each genotype revealed an enrichment for protein serine/threonine kinase activity functioning within the MAPK and/or PI3K signaling pathways. For approximately one third of these events unique to a single genotype, the same transcript was subject to AS in one or more of the remaining genotypes at a different exon. This finding indicates that signaling downstream of the various PDGFR dimers targets an overlapping set of transcripts encoding protein serine/threonine kinases for AS. Together, our results demonstrate that AS is the predominant mechanism of gene expression regulation downstream of PDGFR signaling in the facial mesenchyme.

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