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“Therapeutic and Prognostic Potential of a Novel Signaling Pathway in Colorectal Cancer”

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A long-standing question in the field of cancer cell biology is to understand the interplay between distinct signaling pathways that control tumor cell behavior. The molecular mechanisms by which Wnt/ Frizzled (FZD), growth factor receptor-tyrosine kinases (RTKs) and heterotrimeric G-proteins, three major oncogenic signaling hubs in eukaryotes, relay signals across the plasma membrane independently of each other have been extensively characterized. We have recently characterized a multimodular signal transducer, DAPLE, which operates at the crossroads of all three pathways: 1) it binds FZD-receptors and Dishevelled, a key component of Wnt signaling; 2) it is a guanine nucleotide-exchange factor that activates heterotrimeric G α -proteins, and 3) it is a substrate of multiple growth factor RTKs and non-RTKs. Daple is a double-edged sword; it suppresses tumor formation in the normal epithelium and in early-staged cancers but fuels EMT and invasion in advanced cancers. Using the powerful synergy of cell biology, biochemistry, chemical and peptide therapeutics on zebrafish tumor xenograft models and biomarker studies on patient cohorts, here we will dissect how DAPLE integrates G-protein and phosphotyrosine-based signals to stimulate Wnt signaling during cancer initiation/progression. Findings will advance our knowledge on the convergence of signals through DAPLE and may unravel ways to exploit DAPLE for therapeutic and/or prognostic purposes.