Development results from tightly controlled gene expression driven by the activity of transcription factors (TFs). As such, TF activity is highly regulated, integrating inputs across multiple regulatory levels to impact developmental outcomes. In plants, this is exemplified by CLASS III HOMEODomain-LEUCINE ZIPPER (HD-ZIPIII) proteins, a >700 million-year-old family that arose before the common ancestor of Chlorokybus algae and land plants. HD-ZIPIII TFs were then repeatedly coopted to regulate pivotal developmental innovations including stem cell niches, lateral organs, and vasculature. HD-ZIPIII activity is regulated by multiple mechanisms, including the miRNA mir166 and the LITTLE ZIPPER (ZPR) family of microproteins. HD-ZIPIII proteins also contain a START domain. Initially identified in animals, START domains adopt an α/β helix-grip fold, creating a hydrophobic pocket which accommodates lipophilic ligands ranging from long-chain fatty acids to sterols to isoprenoids. Remarkably, the impact of the HD-ZIPIII START domain remains unknown, despite their essential roles in development and molecular identification over twenty years ago. Using PHABULOSA (PHB) as a representative HD-ZIPIII protein, we demonstrate that the START domain renders HD-ZIPIII dimers competent to bind DNA, while increasing both their frequency and transcriptional potency. The developmental and evolutionary implications of these findings will be discussed. I will also briefly discuss our efforts to use flat leaf production as a model to identify determinants and relationships that lend robustness to the complex process of development.

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