Widespread conservation of developmental regulation of alternative splicing in mammals

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Alternative splicing (AS) allows single gene to produce multiple mRNAs and, consequently, proteins. AS is very abundant in eukaryotes, especially in mammals. Recent studies have shown its involvement in development, stress response, and disease. Contrary to the evident functionality of AS, recent studies revealed an overall low conservation of AS in adult organs. To solve this puzzle, we investigated the evolution of AS regulation during embryonic and postnatal development of seven tissues in six mammals and a chicken based on RNA sequencing data for a total of approximately 2,000 samples. Our results show that developmental AS changes are highly tissue-specific and mostly occur in brain, heart, and adult testis. We discovered two distinct brain-specific regulatory programs that are specific to pre- and post-natal stages, respectively. In most cases, we observed two tissue-specific patterns: the first one corresponds to tissue-specific exon inclusion, the second one to tissue-specific exclusion. Strikingly, inclusion patterns are more conserved, associated with more regulatory elements and exhibit stronger functional enrichment than exclusion patterns. In brain and heart these mirrored patterns also exhibit mirrored positioning (relatively to the exon) of regulatory elements in pre-mRNAs. Though we analyzed all species separately, most of patterns were observed in all species, that points to prominent conservation of developmental regulation of AS. Strikingly, same patterns encompass orthologous exons in different species. The aforementioned patterns exhibited conserved association with many specific sequence motifs. Most of them were not associated with any known RNA-binding proteins.