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The consequences of alternative splicing on biological pathways

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Short Abstract: We evaluated the consequences of alternative splicing on biological networks using ENSEMBL. 3910 of 21205 human genes produce two or more proteins with different domain compositions. According to domain network analysis, at least 490 of 2450 protein interactions surveyed would be lost for loss of a critical domain.

Long Abstract:

Higher-order eukaryotes present biologists with complexities not found in simpler organisms. One such complexity is alternative splicing. 7085 of 21025 human genes in ENSEMBL encode two or more different proteins, with 3910 genes encoding proteins with different domain compositions. We evaluated how this change in domain composition may modulate biological networks.

First, in regulatory networks, alternative splicing often produces transcription factor proteins with no DNA binding domains. For example, in 438 of 3910 genes, some protein isoform lacks a zinc finger domain present in others. In many well-studied cases, when a DNA binding domain is spliced out of a transcription factor protein, it interacts with most of the usual co-factors to form a transcription factor complex, but a complex that cannot bind DNA. Such proteins not only produce no transcription, they absorb low-abundance co-factors; thus, the loss of a DNA binding domain can transform a transcription activator into a transcription repressor.

Additionally, when a domain is spliced out of a protein, certain protein-protein interactions may cease to occur. We evaluated the frequency of this using domain network analysis; given an interaction between two proteins, domain network analysis identifies the protein domains most likely to interact. We evaluated the frequency of this using interaction data from the Rual human interaction dataset. Out of 2450 interactions studied, 490 show evidence suggesting that domain loss through alternative splicing would effectively cancel the interaction.

Most biological network modeling relies on microarray data to assess when a gene is expressed. Domain-level changes in splicing cannot be seen with traditional microarrays, which measure overall expression levels; alternative splicing microarrays offer improvements, but involve greater analysis complexity. Thus, we must consider what measurement platforms are most appropriate for our questions. Furthermore, where a gene's products differ in their interaction patterns, and thus their effect, we must reconsider our assumptions on "gene function".