The consequences of alternative splicing on biological pathways

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Higher-order eukaryotes present biologists with complexities not found in simpler organisms. One such complexity is alternative splicing. 7179 of 22218 human genes in ENSEMBL [1] encode two or more different proteins, with 2229 genes encoding proteins with different Pfam [2] domain compositions. We evaluated how these changes in domain composition may alter biological network behavior, a phenomenon suggested to be frequent in prior work [3].

First, in regulatory networks, alternative splicing can change the DNA-binding affinity of transcription factors by altering the number of DNA-binding domains, a pattern also observed by others [4]. For instance, in 265 of 563 genes producing zinc finger proteins, alternative splicing alters the number of zinc fingers. In extreme cases, this can lead to a complete loss of DNA-binding. For example, the Icaros gene can produce a dominant negative transcription factor protein: it cannot bind DNA but binds other co-factors, thus competing for low copy-number co-factors and consequently acting as a transcriptional repressor [5].

Additionally, when a domain is spliced out of a protein, some protein-protein interactions may cease to occur. Using Cytoscape [6] with the DomainNetworkBuilder pluign [7], we evaluated the frequency of such potential interaction loss. Out of 2450 interactions from the Rual human interaction dataset [8], 493 show evidence suggesting that domain loss through alternative splicing would effectively cancel the interaction.

In summary, we observed many genes for which alternative splicing may change network topology by changing protein domain composition. Network activity is generally assessed using microarray data, but traditional microarrays measure overall gene expression and thus cannot detect changes in domain composition. Alternative splicing microarrays offer improvements, but involve greater analysis complexity. Thus, we must consider what measurement platforms are most appropriate for our specific analysis questions. Furthermore, where gene products differ in their roles within biological networks, we must reconsider our assumptions on “gene function”.

References

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