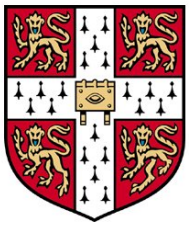
# Mechanisms of change in protein architecture



Marija Buljan

Trinity College

University of Cambridge

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"*Well begun is half done.*"

Aristotle

# Declaration

The work presented in this dissertation was carried out at the Wellcome Trust Sanger Institute between May 2006 and September 2010. This dissertation is the result of my own work. No part of this dissertation or anything substantially the same has been or is being submitted for any qualification at any other university.

# Summary

Proteins are the basic building blocks and functional units in all living organisms. Moreover, differences between species can frequently be explained with differences in their protein complements. Importantly, proteins are often composed of segments, i.e. domains that have a certain level of evolutionary, structural and/or functional independence. The majority of proteins in nature contain two or more domains, and an individual domain can often occur in combinations with different domain partners.

In the first part of my thesis, I traced the history of animal gene families and the proteins these genes encode. By this means, I was able to infer events where changes in protein domain architectures took place. This showed that both insertions and deletions of single copy domains preferentially occur at protein termini, but also that changes are more likely to occur after gene duplication than organism speciation. Finally, domains that were most frequently gained were the ones that are related to an increase in organismal complexity, thus underlining the important role of domain shuffling in animal evolution.

In the second part of my thesis, I focused on a set of high confidence domain gain events and investigated the evidence for molecular mechanisms that caused these domain gains. In agreement with observations from the first part - that changes preferentially occur at the termini - I have found that the strongest contribution to gains of novel domains in proteins comes from gene fusion through the joining of exons from adjacent genes into a novel gene unit. Two other mechanisms that have been suggested to play a major role in the evolution of animal proteins, retroposition and middle insertions through intronic recombination, have a smaller role in comparison to gene fusions. Since the majority of these domain gains are again observed after gene duplication, this suggests a powerful mechanism for neofunctionalization after gene duplication.

Finally, in the last part of my thesis, I address a mechanism that increases the number and variety of proteins in an organism – alternative splicing. In particular, I investigate the functional consequences of tissue-specific alternative splicing events. I found that tissue-specific splicing tends to affect exons that encode protein regions without defined secondary or tertiary structure. Importantly, it is known that these disordered regions frequently play a role in protein interactions. In agreement with this, I observed significant enrichment of tissue-specifically encoded protein segments in disordered binding peptides and posttranslationally modified sites. A possible result of the finely regulated alternative splicing of these segments is a tissue-specific rewiring of protein network. In conclusion, both alternative splicing and domain shuffling can increase proteome diversity. However, a protein with a new function can often directly or indirectly shape the functions of other proteins in its environment.

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