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Mutations at protein-protein interfaces: Small changes over big surfaces have large impacts on human health

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ABSTRACT

Many essential biological processes including cell regulation and signalling are mediated through the assembly of protein complexes. Changes to protein-protein interaction (PPI) interfaces can affect the formation of multiprotein complexes, and consequently lead to disruptions in interconnected networks of PPIs within and between cells, further leading to phenotypic changes as functional interactions are created or disrupted. Mutations altering PPIs have been linked to the development of genetic diseases including cancer and rare Mendelian diseases, and to the development of drug resistance. The importance of these protein mutations has led to the development of many resources for understanding and predicting their effects. We propose that a better understanding of how these mutations affect the structure, function, and formation of multiprotein complexes provides novel opportunities for tackling them, including the development of small-molecule drugs targeted specifically to mutated PPIs.

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1. Protein-protein interactions at the molecular level

Interactions between proteins mediate many biological processes, especially with respect to cell regulatory events requiring high signal-to-noise ratios to transduce information within and between cells (Blaszczyk et al., 2015). Fig. 1 shows an analysis of the range of biological processes in which PPIs are involved in humans. Heavy PPI involvement in critical cellular processes such as metabolism, cell signalling and cell death is indicative of why disruption or stabilisation of PPIs can have significant biological consequences and play roles in the development of diseases such as cancers (Fry and Vassilev, 2005). Residues

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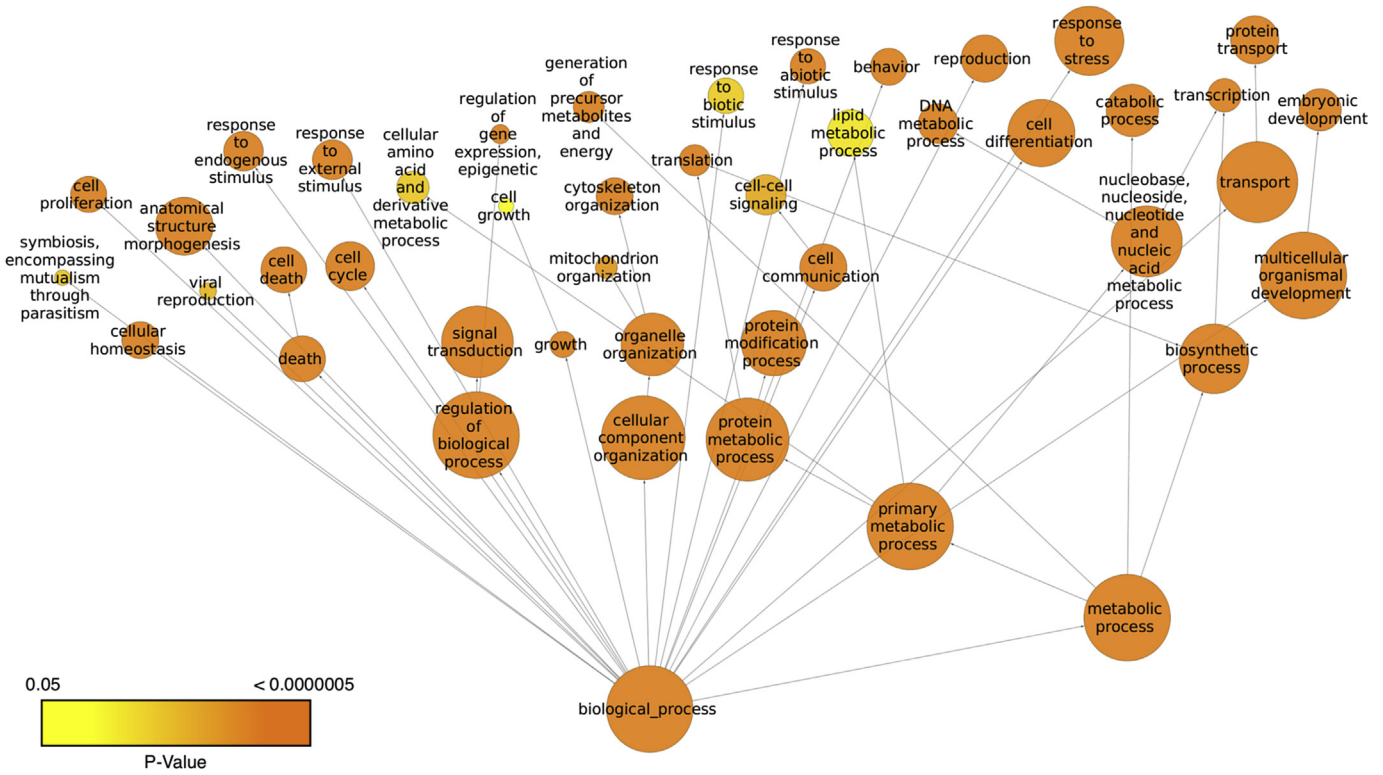

Fig. 1. GOslim term enrichment in the Homo sapiens protein-protein interactome The hierarchical, directional network spanning out from biological process reflects Gene Ontology (GO) (Ashburner et al., 2000; The Gene Ontology Consortium, 2015) biological process terms that were over-represented in a human PPI network constructed from the mentha (Calderone et al., 2013) and HPIDb (Kumar and Nanduri, 2010) databases. Node size was determined by the proportion of genes in the PPI network covered by the GO term. Node colour reflects the adjusted P-value indicating the significance of the over-representation of the term within the PPI network. Generated using the Cytoscape (Shannon et al., 2003) BiNGO plugin (Maere et al., 2005).

involved in protein interactions are under additional evolutionary restraints, and are more highly conserved than surface residues (Chelliah et al., 2004; Innis et al., 2000). It is therefore not surprising that mutations at PPIs are associated with a broad range of diseases. More surprising however is that recent reports show that mutations at PPIs are over-represented amongst disease-causing mutations (David et al., 2012; Engin et al., 2016; Yates and Sternberg, 2013). This raises an interesting idea that mutations affecting PPIs may allow for biological activities to be modulated, causing a disease phenotype, but with a smaller fitness cost compared to the catastrophic effects on protein function caused by many active site or protein-destabilizing mutations. Understanding how mutations modulate protein interactions and thus biological functions raises potential for developing therapeutic interventions targeting interaction mutants.

Protein interactions impart selectivity and sensitivity to biological processes, and may occur either through the co-operative assembly of specific multi-protein assemblies or through the co-operative folding and binding of one binding protomer onto another. The traditional view of protein interaction interfaces (the molecular surfaces through which subunits of multiprotein complexes make contact with one other) as being large, uniformly flat, and chemically featureless, has evolved. Recent studies highlight that interactions involving cooperative folding and binding of small polypeptides make use of distinct concavities (“pockets”) as opposed to the large single volume pockets exploited by small-molecule drugs (Jubb et al., 2015). Furthermore, interactions between larger, globular proteins, while utilising flat binding surfaces overall, make use of small loci of well-defined interaction sites within their large, flat interacting surfaces, even if only via small but well defined pockets fitting a single residue (Jubb et al., 2015). Highly shape and chemically-complementary single residue interactions have been shown to be “anchoring” points in many PPI interfaces (Koes et al., 2012; Koes and Camacho, 2012; Li et al., 2004; Rajamani et al., 2004), and can be important energetic drivers, or “hotspots”, in the assembly of PPI interfaces (Bogan and Thorn, 1998; Clackson and Wells, 1995). The observation that PPI interfaces can have these specific residues or regions that disproportionately drive protein complex assembly has spurred not only in an interest in developing drugs to target these interactions (Winter et al., 2012), but also an appreciation that single mutations can have a significant effects on protein-protein binding affinity. However, it is important to note that assessments of PPI affinity and the impacts of mutations on protein stability and PPI affinity, are complicated by the natural affinity of the interaction and whether the interaction is transient or constitutive/obligate (Liang et al., 2016; Nooren and Thornton, 2003). This can be related to function (Acuner Ozbabacan et al., 2011; Blundell et al., 2000; Perkins et al., 2010), and are important considerations when considering the known and potential impacts of mutations.

2. Mutations altering protein-protein binding affinities: implications for human health

The prevalence of PPIs (Strong and Eisenberg, 2007; Stumpf et al., 2008; Wells and McClendon, 2007) and their importance in a multitude of biological processes (Blundell et al., 2000) make PPIs prime candidates for modulation by disease processes. An especially comprehensive analysis of the structural nature of mutations in cancer has shown that mutations at PPI interface regions play “driver” roles in many cancers, and that specific mutations can herald different patient outcomes (Porta-Pardo et al., 2015). On a