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Intrinsic Protein Disorder as a Drug Target in Oncology: Designing Drugs Targeting Plasticity

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Cancer is gradually becoming the leading disease-related cause of death of the human population. Thus, there is an ultimate need for innovation in drug discovery and development, especially in the area of oncology. Unfortunately, clinical attrition rates are a critical issue in drug development, particularly in oncology where over fourfold higher rates of attrition were determined in respect to other indications [1].

Although, this trend presumably relates to the substantial heterogeneity and the inherent biological complexity of cancer [2], in order to track the source of this failure it should be interesting to chart the drug targets that researchers have traditionally focused on. It could be then realized that one of the fundamental issues that drove to this decline in pharmaceutical research and development is the philosophy that shaped the drug discovery process [3]. The "one-gene-one-disease" theory sculpted the drug design concept to treat diseases by targeting individual chemoreceptors with a "magic-bullet" therapy [4]. Drugs were thus traditionally rationally designed and tailored to target rigid protein binding pockets on the basis of complementarity, the so-called "lock-and-key" mechanism. This unidimensional approach on proteins presenting compact and well-ordered 3D architectures lead presently to the majority of 'druggable' targets: G-protein-coupled receptors (GPCRs) and enzymes [5, 6].

However, more than a third of the eukaryotic proteins contain intrinsically disordered regions [7]. Intrinsically disordered proteins (IDPs) although they lack a well defined 3D structure [8] their functional repertoire complements the functions of ordered proteins [9] and their abundance is tightly regulated in the cell [10]. The structural adaptability as also the lack of architectural ordering in these proteins provide functional unique capabilities to interact with multiple protein partners (network hubs) without sacrificing specificity, in contrast to ordered proteins with well defined architecture that interact mainly with a single protein partner (network ends) [11]. Due to their inherent disorder and plasticity, intrinsically unstructured proteins elucidate important roles in cell-signalling and regulation. Interestingly, proteins associated with various human diseases are enriched in intrinsic disorder, and the disease-related unfoldome has been mapped to cover a significant part of the human proteome [12]. For instance, it was indicated that more than 79% of human cancer-associated proteins contained intrinsically disordered regions [13].

The frequent occurrence of intrinsic disorder in cancer-associated proteins strongly suggests that disorder information should be employed in the drug discovery process towards the development of novel anti-cancer drugs. Unfortunately, this area remained largely unexplored on the basis of the aforementioned philosophy of rational drug design, as also due to the lack of effective screening tools. Although it is very challenging to design small molecules for drug targets that their overall architecture is constantly altered, success could emerge. This was also the case for protein-protein interactions (PPIs), that are abundant in cancer [14] and were originally thought as "undruggable" targets due to the inherent difficulty for a small molecule to compete for binding on such flat and extensive protein interfaces. However, the realization that a centralized region of residues (hot-spots" [15]) encompassed the key interactions to the binding affinity and presents comparable dimensions to the size of a small organic molecule paved the way for the discovery of PPI antagonists [16,17].

Although it is evident that the development of new approaches to discover drug molecules that target intrinsically disordered protein regions should be a high priority, a key question that arises is how drugs can be sculpted for protein targets that undergo "metamorphosis" from one form to the other as IDPs. Since IDPs are tightly regulated and disease conditions emerge due to their altered availability, one could indirectly target them by fine-tuning regulatory mechanisms or enzymes maintaining their homeostasis [18]. Data have now emerged showing that selective blocking of specific interactions of intrinsically disordered TFs with their protein binding partners is possible [19]. Similarly to the disruption of structured PPIs it is of importance to decode hot spots in IDPs. Such hot-spots could be localized hydrophobic clusters in helix-forming molecular recognition elements (a-MoREs). Mimicking these hydrophobic clusters by small molecules could block interaction of the IDP with its structured protein partner [20]. Computational tools have been developed to locate such druggable short disordered binding regions which folds upon binding into a specific structural element [20]. In addition, novel techniques should be developed that will be able to decipher the conformational landscapes sampled by IDPs. NMR spectroscopic approaches based on the recording of pseudo contact shifts and residual dipolar couplings could be very useful in this direction as also to identify hot-spots [21,22]. On the basis of these tools, structural heterogeneity was recently determined in protein complexes [23]. Such disorder information within the protein-biomolecule complex level was generally omitted in former drug discovery efforts. However, since disordered complexes are prone to perform promiscuous contacts leading to pathology, new strategies employing disorder information should be established for the discovery of new drugs. Large scale screening platforms should be also directed in these targets. Natural products that evolved after nature's combinational chemistry to have chemical diversity and interact with multiple biological target molecules might be a good starting point for these screening platforms [24,25]. Taxol, a mitotic inhibitor used in cancer chemotherapy, is a successful paradigm of a natural product that

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interacts with an intrinsically disordered region in Bcl-2, altering the apoptotic signalling pathway.

Given the importance of intrinsically disordered proteins in various human diseases and especially in cancer, an interscience collaboration and integration of data from different omics platforms targeting IDPs can be of unprecedented value towards the development of novel anticancer agents.

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