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PROBING RESEARCH PRECINCTS FOCUSED ON SYSTEMATIC DETERMINATION OF THE BIOLOGICAL EFFECTS OF MACROMOLECULAR INTERACTIONS

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ABSTRACT

The morphological arrangement of interacting chemical groups in a binding or an active site presents an increased magnitude of interaction specificity and affinity which are crucial to biological functionality. The configuration and functionality of macromolecules are influenced via the dynamics of covalent bonds and polarity, bond rotations and vibrations, non-covalent interactions, hydrophobic impact and molecular structure. Macromolecular interactions comprise diverse non-covalent interactions with specificity and precision which are crucial to biological functions. Molecular interactions are the crux of all cellular processes, viz: catalysis, recognition and signal transduction, whereby several diseases or disorders can be directly associated with aberrant interactions between molecular pairs which provide the latitude for drug design capable of reversing aberrant biophysical features. Sedimentation rate, as a physical method and sophisticated technique is used to investigate macromolecular interactions that necessitates optimum precision in both experimental design and data analysis. The kinetic analysis of an expansive array of macromolecular interactions with evolving of experimental design and data analysis provide for accurately defined assembly of mechanisms and rate constants correlated with macromolecular interactions.

KEYWORDS: bonding, cellular processes, human diseases, experimental designs, targets, spatiotemporal variations, drugs

1. INTRODUCTION

Macromolecules are highly dynamic and regulated biological entities (Chukwuma 2019a). Various experimental and computational procedures are utilised quantitatively in the determination of their roles. Biological macromolecules include carbohydrates (Chukwuma 2017a), lipids (2019b, c), proteins (2020a, b) and nucleic acid (2020a, b) (Chukwuma 2016) several essential nutrients, polymers, and monomers which are necessary for life. In essence, biological macromolecules are intricately complex, large and exhibiting basic molecular units, such as amino acid, nucleotide, and sugar polymers to form proteins, nucleic acids and carbohydrates, respectively; as well as varied modular components to constitute lipids. The biosynthesis and degradation of biological macromolecules involve linear polymerization, and

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breakdown steps for proteins, nucleic acids and lipids, as well as branching/debranching regarding carbohydrates. The processes ostensibly involve multi-protein complexes as observed in ribosomes and proteasomes in complex regulatory roles (Chukwuma 2020a, b).

Covalent and non-covalent bonding dynamically effect the three-dimensional protein and nucleic acid functionalities. The amino acid sequences as depicted in nature are specific for their biological activities, but do not essentially impact the discrete folded structures. The morphological dynamics of these macromolecules (Chukwuma 2019a) correlate to covalent bonds and polarity, bond rotations and vibrations, non-covalent interactions, hydrophobic effect and molecular structure. The sequence and morphology of proteins and nucleic acids can be altered via alternative splicing mutations or chemical modifications to evolve into novel biological roles (2020a, b).

Macromolecular interactions are influenced by weak, non-covalent bonds

Defined macromolecules are inextricably linked in the catalysis of chemical reactions or facilitate processes, such as molecular transport. These processes are quantitatively correlate by rate laws and thermodynamic principles, such as collision theory, transition state theory, rate laws and equilibria, and the corresponding effects of temperature, structure and chemical reactions (Chukwuma 2016, Chukwuma 2019a). Macromolecular interactions with other molecules are influenced by the same weak, non-covalent interactions which mainly function to mantain the three-dimensional structures of macromolecules, especially as evident in hydrogen bonding, hydrophobic effect, and ionic interactions. The interactions between proteins are the most ubiquitous and possibly the predominant family of interactions within biological macromolecules. This is in part due to the well-established diversity of cell protein constituents. The diversity of lipids, carbohydrates and nucleic acids is ostensibly relevant, but proteins perspicuously have elevated profile as specific biological carriers. Also, the diversity of protein structure and function is less difficult to determine in contrast to the more latent variations which relate to the specificity of other macromolecules (Markey 2009). Thus, several biomolecular interactions investigated with optical biosensors are inextricably linked with protein-protein binding. The technique is useful in the monitoring of any molecular interactions, and studies associated with nucleic acids (Chukwuma 2020a, b). The assemblage of functional groups on a conventional protein molecule allows for strategic selections for the attachment of interactants to the sensor surface extending from amine- or thiol-based chemical coupling to specific high-affinity capturing methodologies (Markey 2009). Proteins are usually relatively large molecules with relative molecular mass from tens to hundreds of kilodaltons. Therefore, the mass content detection from surface Plasmon resonance (SPR) is higher than the instrumentation detection limit. Membrane-linked proteins can be embedded in lipid layers on the sensor surface to conserve the integrity of the hydrophobic milieu. Several protein-protein interactions are susceptible to disruption via exposure to less adverse ambient for efficient and effective regeneration (Markey, 2009).

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Due to the accelerating number of experimentally defined structures of macromolecular complexes, it is perspicuous that the interactions associated with protein structures are mediated not merely as diverse non-structured regions, such as interdomain linkers or terminal sequences. These complexes are collated as databases following expansive analysis of pertinent attributes whereby the interactions which constitute the complexes are grouped correlating to their structures and functions (Kuang et al et al., 2011).

Lipids are of significance in the structural integrity of biological membranes, and provide specific dynamic features to the bilayer. They have conventionally been observed as passive membrane components, and inclusively, in a more established function as second messengers in signal transduction pathways. Findings accumulate that lipids are sorted along membrane traffic routes, and are directly related to the regulatory mechanism of membrane sorting, membrane flow,and possibly in the endocytic pathway (Kobayashi et al., 1998).

Biological processes rely on the interactions of other macromolecules and certain smaller ligand effectors for a specific, precise and regulated activity. Sometimes, the interactions are durable, whereas atimes, they constitute transient mechanisms for optimum regulatory biological roles. Specific ligand macromolecular interactions and/or conformational transitions are perspicuously correlate to other similar macromolecules as partners and present multiple equilibria. Elucidating the forces defining these processes of multiple equilibria in the stabilization and control of the function of macromolecules, it is pertinent to study the energetic, thermodynamic stabilities and affinities, binding kinetics and mechanisms, enzymatic catalyzation as well as both steady and transient/pre-steady state modalities.

Analysing cellular processes and drug targets

Thus, molecular interactions pivot all cellular processes, viz: catalysis, recognition and signal transduction, whereby a vast majority of diseases may be directly associated with aberrant interactions between molecular pairs which allow for drug designs capable of reversing perturbed biophysical attributes. Remarkable experimental and computational scientific studies have been realised pertaining individual proteins with small molecules, numerous protein-protein (PPs) (Chukwuma, 2019d), and protein-nucleic acid (PNs) (Chukwuma, 2020a, b) interactions which are indirectly linked with aberrant signaling and emerged as drug targets. PP interactions form viral therapeutic targets, but there have been impediments in the design of potent inhibitors to explicitly constitute a blockade to overcome these interactions. These constraints and challenges emanate from the inability to surmount the binding energy related to PP interactions by a small molecule and to focus on the plethora of ostensibly diffuse interacting surfaces which are generally without specific portions or areas wherein small molecules are targets. Targeting allosteric sites gives the latitude for greater specificity, and definitely expunges the competitive criterion of a protein-binding partner. This is designed to invariably partner with allosteric sites on another

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protein for specific interacting entities, if the other proteins are perturbed. Instances abound, such as covalent inhibitors which target the activated interacting mechanisms Ga-subunits and the regulators of G-protein signaling (RGS) proteins. With the slow off-rate of these inhibitors, there is pertinence for designing more potent small molecules which can partner non-covalently, and gain identical measure of potency and specificity as their covalent partners; and for identical inhibitors to present disparate reactions with homologous proteins. It is suggested that the underlying dynamics of such proteins are ostensibly atypical and depict distinctiveness. Rather than 'structure-based drug design', a novel 'dynamics-based drug design' modality predominates to target macromolecular interactions by employing small molecules as chemical probes (Arkin et al., 2014; Atilgan et al., 2004).

An analysis characterizing protein-protein (PP) interfaces with identification of relevant residues at the interfaces of complexes by employing protein contact network strategy, with flexible, global and local topological characteristics of each protein contact network was computed (Di Paola et al., 2015). In the study, crystal structures of unbound anthrax PA, octomeric PA, PA-PA-LF forms, and complexes of CMG2 complexes were employed for the identification of residues/hot spots which significantly impact complex stability. Results showed that PP interface attributes were expansively independent of global system typology descriptor, thus requiring extensive analysis of local/single residue. As the most paramount for global stability, network vulnerability assessment measured elevated P residues which were spread both at PP interfaces and sites distant from PP interfaces. It is suggested that explicating the high protein residues which are relevant for supramolecular interactions present an encompassing application for site-directed mutagenesis and other experimental modalities directed at functionality characterization of PP interfaces. The modality will be of importance for medicinal chemists to identify lacunae in molecular-docking studies as to effectively and efficiently design drugs which correlate PP interactions. Establishment of augmented protein residues ostensibly unravels extended channels to drug leads, as to bind allosteric site, influence supramolecular interactions, with efficacy similar to or more potent than drugs directed at merely PP interfaces (Cheng et al., 2015; Di Paola et al., 2015).

Simulations of molecular dynamics formulate potent strategies to study biomolecular conformational modifications or protein-ligand, protein-protein, and protein-nucleic acid interactions. Direct applications are usually impaired by inchoate sampling strategies because in a commonly simulated pathway, the system dissipates abundant time and resources encapsulated by high energy barriers in limited sites of the configuration milieu. A plethora of procedures have been employed to overcome the constraint and induce space sampling strategy. Temperature Accelerated Modular Dynamics/TAMD, Logarithmic Mean Force Dynamics/LogMFD, and Multiscale Enhanced Sampling/MSES algorithms have been employed paradigmatically to enact reaction modalities for the latitude to accelerate sampling of significant precincts of the force-energy landscape via automatic exploration (Fujisaki et al., 2015). The correlating attribute

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of these strategies is the dependence on the extended phase space of the instant physical system via enhancement with a set of variables or dynamical variables which are related with the system through collective variable activities of the physical coordinates. The setting provides for efficient collective variable space exploration of the free energy landscape of the original system concerning the collective variables. The different methods achieve this exploration through disparate pathways. In TAMD, the collective variables evolve at an elevated temperature than the physical variables for efficient crossing of free energy barriers higher than the physiological temperature. In LogMFD, a logarithmic free energy transformation is associatively applied with the conserved quantity derived from deterministic dynamics for direct reconstruction of free energy as collective variables evolve. For MSES, it correlates as a potential model intended for the collective variables and inexact replicas of the extrapolated system utilized in a replica exchange framework, each with a unique value of the coupling parameter between the original system and the collective variables. The statistical attributes of the unbiased physical system is in conformity with the reconstruction of the replica with zero coupling (Fujisaki et al., 2015).

Heterotrimeric G-protein signaling was shown to modulate several intracellular signaling pathways and the mitogen-activated protein kinase (MARK) family. The role of one MARK family class, c-Jun N-terminal kinases (JNKs) is associated with G-protein coupled receptors (GPCRs) activation at the plasma membrane. Application of a discrete set of G-protein signaling techniques depicted that subcellular domain-specific JNK activity is inhibited by Gai1 activation, the Gai isoform located in enormous quantities within intracellular membranes, such as the endoplasmic reticulum – Golgi complex interface, and their related vesicle pools. Intracellular Gai regulators, G-protein signaling3 (AGS3) activator and the G-protein signaling protein 4 (RGS4) regulator pose a remarkable impact on the JNK activity regulation. These data suggest extant specific intracellular signaling complex which control JNK activity entrenched within cells. The study suggests unraveling of a novel functionality for Gai3-mediation in mammalian cells as a specific inhibitor of JNK activation and signaling via receptor-independent GEF activity on intracellular membrane pools with resultant inhibition of local JNK activation. This definitely characterizes the novel protein complexes controlled via heterotrimeric G-proteins localized in intracellular membrane pools within cells and distal to the regulatory activities of numerous external GPCRs. The features of receptor-independent G-protein activation, signaling and its association with cellular health processes and homeostases depict as sustainable investigation trajectories with potential to unravel novel cellular activities for Ga subunits as well as their intracellular binding partners and effectors (Bastin et al., 2015).

Aberrant assemblage and dynamics in protein-protein interactions excoriate the networks of protein-protein interfaces culminating in human diseases or disorders. Despite the challenges and constraints regarding topologies of the relatively large surfaces of protein-protein interfaces being deeply buried, it is

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clear that recent advances in techniques, such as chemical screening, improved structural and computational biology have obviated certain challenges and unraveled the conduit to chemical modulations. Allostery has produced robust changes in protein-protein interactions defying constraints and challenges. One protein-protein interface can propagate changes via expansive web of interactions; thus, with combined directed and propagated impacts on protein-protein interactions, networks could feature in future roles of molecules in biology (Cesa et al., 2015).

The potential target sites of a feeble protein-protein interface was identified in the analysis of the fracture mechanisms of the Norwalk viral capsid structure with potential sites to inhibit uncoating by stabilization of the labile interface using atomic force microscopy nanoindentation experiments to unravel aetiologies of debilitating gastroenteritis devoid of any extant anti-viral therapy. The infection process involves protein capsid uncoating with exposure of the viral genome that allows for viral replication (Boyd et al., 2015).

Aptamers are short nucleic acids (Chukwuma 2019d) which fold into atypical three-dimensional configurations and drive binding of a specific target. The aptamer structure, such as stem-loops, g-quadruplexes, and pseudoknots functions on its potential in the recognition and discrimination of specific targets. Tremendous advantages are observed in comparison of aptemers to antibodies due to feasibility, production costs and absence of immunogenicity. The generating of aptamers is due to evolved systematic ligand via exponential enrichment. Aptamers have developed towards a range of targets, such as proteins, small molecules, intracellular targets, cell surface receptors and complete cells, with resultant therapeutic outcome. Despite the technical constraints and challenges, intellectual property landscape has harnessed the advancement of aptamers for direct therapeutic application. Aptamers have been advantageous in conjugate utilization for targeted delivery of concomitant therapeutic molecules in newfangled sophisticated devices for monitoring and detection as biosensors, diagnostic imaging and nanomachinery (Rodesh et al., 2014).

Natural modalities in the interference with molecular interactions involves the entrapment of macromolecules in transition states with corresponding partners in dead-end complexes which are deficient in accomplishing their biological activity. This characteristic inhibition is referred to as interfacial inhibition, as illustrated by two natural inhibitors, brefeldin A (BFA) and camptothecin (CPT). Regarding BFA, interfacial inhibition occurs at the PP interface, but in the aspect of CPT, it occurs at the PN interface. Concerning both systems, the drugs are easily facilitated in transient structural and energetic milieu of the macromolecular complex as “hot spots” for drug binding. Also, several natural compounds, such as forskolin, tubulin inhibitors and immunophilins target protein interfaces. These provide for interfacial inhibition as a paradigm for drug discovery or leads (Chukwuma 2020b) in the interference of

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macromolecular complexes (Pommier & Cherfils, 2005). Appreciatively, the targeting of macromolecular interface is a conventional trajectory natural product to drive the activation of macromolecular complexes via the stabilization of normal transient intermediates (Pommier et al., 2015).

Applicable tools to explicate macromolecular interactions

Sedimentation equilibrium is a sophisticated technique used to study macromolecular interactions. It necessitates optimum precision in both the experimental design and data analysis. The complexity of the interacting system for the analysis is ordinarily restricted by its ability to deconvolute the exponential contributions of all available species to the cumulative concentration gradient. This is realised partly via the application of multi-signal data collation and implementation of soft mass conservation. The outcome is robust data analysis, if procedures such as isothermal titration calorimetry and sedimentation velocity are included (Ghirlando, 2011).

A viable method is biolayer interferometry (BLI) that allows for direct determination of biomolecular interactions in real time without relying on labeled reagents. An augmented usage of BLI methodology extrapolated from atypical biopharmaceuticals to monitoring of infectious diseases provides for expansive application of the procedure in the life sciences (Kumaraswamy, 2015).

Analytical ultracentrifuge sedimentation involves a matrix free-solution method that functions without immobilization, columns, or membrane, It is used for the investigation of self-association and complex or hetero-interactions, stoichiometry, reversibility and interaction integrity of a broad spectrum of macromolecular species and encompasses an expansive dynamic extent of dissociation constants ranging from 10-12 M to 10-1 M (Harding et al., 2015). Advances have occurred in sedimentation velocity and equilibrium as applied to protein interactions and mucoadhesion, protein self-association in tetanus toxoid and afrin, protein-like carbohydrate association for amino-celluloses, carbohydrate-protein interactions in polysaccharide-gliadin, nucleic acid-carbohydrate for xanthan-chitosan and tertiary polysaccharide complex interactions (Harding et al 2015).

Dynamics and kinetic analysis

The universal application of biosensors in the characterization of biomolecular interactions has accelerated. These tools provide information in the energetics of macromolecular interactions devoid of labeling. Although, commercial technologies such as BIACORE facilitate utilization, the extraction of accurate rate constants for a reaction needs optimum experimental and robust data analysis methodology (Myszka, 2004). BIACORE biosensors may be required to determine reaction kinetics and affinity constants in molecular interactions, but a constraint ostensibly peculiar to the flow system in these tools is that the conventional injection procedures restrict the available time to obtain association-phase data

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(Myszka et al., 1998). Biosensors are biophysical tools for the determination of equilibrium constants and kinetic rate constants in binding situations. On the measurement of reactions at differential temperatures, there is ample latitude to derive thermodynamic data depending on the system. A model system correlating the interaction of interleukin 2 (IL-2) ligand with a receptor subunit suggested that BIACORE constitutes a potent tool in the determination of the reaction kinetics and equilibrium constants in biological molecules (Myszka, 2004). Therefore, advances in techniques for data collation provide for remarkable biosensor data quality, as the potential to define binding data using simple interaction models, undergirds validity to sensors as veritable tools for kinetic analysis. The establishment of attributes of temperature-dependent reactions facilitates the availability of certain thermodynamic information related to the binding reaction. Cooperatively, kinetic and thermodynamic information may elucidate particulars or incidents of biomolecular recognition (Myszka, 2004).

Surface Plasmon resonance-based biosensors distinguish the kinetics of an expansive array of macromolecular interactions undergirded with evolving experimental design and data analysis. They enhance veritable definition of the assembly mechanisms and rate constants related to macromolecular interactions (Myszka, 1997). A marked limitation in the postgenomic period is defining proteome interaction, such as protein-protein (Chukwuma, 2019d) or protein-nucleic acid (Chukwuma, 2020a, b) interactions. Surface Plasmon resonance (SPR) constitutes an optical technique in analyte binding to the surface for modification of the refractive index at the surface/solution interface. Analysis of macromolecular interactions in real time is conducted devoid of a labeling dimension. The extant constraint to SPR imaging is the small number of reactions analysed concurrently. The throughput of SPR imaging was enhanced by using the technology and imaging system. Interaction between p53 and DNA was selected to validate the assay modality. In the presence of a tagged DNA, multiple DNA sequences were targeted on a single chip. Monitoring of the interaction between p53 and the DNA sequences was done by SPR imaging. Quantitative and qualitative analyses depicted identical findings when compared to conventional tools (Maillart et al., 2004).

TOOLS FOR CLINICOPATHOLOGICAL FEATURES

Human diseases are conventionally the resultant impacts of the contributory measures of a plethora of untoward processes (Chukwuma 2017b, c). At the molecular platform, these processes are driven by a complex network of interactions. Thus, a plethora of cerebral pathologies correlate with hepatic deterioration, however, a direct associative etiologic factor remains undeciphered. Utilization of traceable lipopolysaccharides, LPS depicted that drainage of inflammatory macromolecules from the cerebral apparatus result in remarkably preponderant macrophage peripheral infiltration into the hepatic organ independent of Kupffer cells (Yang et al 2020). It was further enunciated that the macrophage conscription was undergirded by signaling from the cytokine IL-34 and Toll-like receptor adaptor MyD88, and

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conducts coordinatively with neutrophils. The findings suggest circulation of brain-derived components to function as an accelerated communication trajectory from the central nervous system to the hepatic apparatus. Elucidation of the manner whereby the central nervous system correlates with the periphery in precarious situations may provide novel paradigms to predict, detect and manage clinicopathological features of the central nervous system (Yang et al 2020).

A computational technique to predict drug target interactions, DTIs has evolved to become indispensable in drug leads or discovery. It diminishes the exploratory ambient for interactions by unravelling potential interaction competitors for veracity via wet-lab experiments which are popular for their exhorbitant costs and time-consuming attributes (Kaushik et al 2020). Chemogenics is an emerging research precinct focused on the systemic determination of the biological effect of an expansive spectrum of minuscule relative molecular mass ligands on an expansively well-endowed macromolecular target spots. Furthermore, with spatiotemporal advances, the sophistication of the algorithms is incessantly increasing and allowing for the ingress and accommodation of large data technologies such as Spark (Kaushik et al 2020). These may provide the latitude, opportunities and environment for further improvement of the interaction of drug targets, project enactment and correlated research objectives. Numerous similarity-based, network-based, machine learning, docking and hybrid strategies to predict the macromolecular targets of minute molecules are extant and constitute veritable technologies in early drug leads and discovery (Chen et al 2020). Due to the increasing advancement of target prediction tools, the scope has been extrapolated to include challenging and structurally complex natural products and macrocyclic minuscule molecules.

DISCUSSION

Biomedical studies in the study of life, disease, and mechanisms of metabolic processes, the ability and potential to access information as well as structure and function of biological macromolecules have increased in leaps and bounds (Chukwuma 2017b, c). These are relevant for future research in macromolecular interactions, such as protein-peptide, protein-oligonucleotide, and other interfaces encountered in human cells for the regulation of gene expression, cell growth and development, cellular proliferations and other highly sensitive molecular interactions.

Macromolecular interactions, such as protein-protein interactions (Chukwuma 2019d) are dependent on precision and time-related attributes as well as underlying cellular functionalities. The binding affinity encompasses the interaction potential translated into physic-chemical features in the dissociation constants (Kd), as the latter is an experimental approach that correlates as an interaction is constituted in solution. The theoretical modeling associated with these interactions is subjected to an integrative trajectory that integrates macromolecules, such as protein-protein recognition (Kastritis & Bonvin, 2013). The

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biophysical research of these macromolecular interactions correlates to the determination of both the interaction affinity and the stoichiometry of the complexes invariably via concentrations of free and bound species. Conventional strategy for the investigation activities of these reversible reactions involve analytical ultracentrifugation, differential scanning calorimetry, surface Plasmon resonance, equilibrium dialysis, diverse spectroscopic techniques, and computational tools for data analysis (Correlia et al 2009; Ghirlando 2011; Chukwuma 2016; Chukwuma 2017b).

CONCLUSION

Macromolecular interactions encompass protein-protein, protein-carbohydrate, carbohydrate-lipid, protein-lipid, protein-nucleic acid, and nucleic-nucleic acid interactions which are crucial to all cellular processes. Elucidation of their characteristics, knowledge and understanding has expanded tremendously due to intensive and extensive research in biochemistry, drug leads and discovery for the benefit to Man and Society.

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