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# A Conspectus on Macromolecular Interactions In Health And Disease

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Abstract: ***To understand human disease process, it is necessary to explicate the structure and function of macromolecules and macromolecular interactions which culminate in disease, and in health. The potential of a cell is undergirded and controlled by a network of molecular interactions. The identification and characterization of cell macromolecular interactions, as well as their structure and function are important to comprehend the underlying causes of disease in humans.***

**Keywords:** health, disease, macromolecules, interactions, methods, mechanisms.

## 1. Introduction

In order to comprehend human disease processes, it is pertinent to grasp the structure and function of macromolecules and macromolecular interactions which result in disease. Organisms react to their ambient due to activation of signaling pathways which result in specific cellular responses. The responses are conducted by macromolecular interactions, with untoward signals culminating in cellular dysfunctions and disorders. The identification and characterization of cell macromolecular interactions using biophysical and other analytic methods are important to comprehend the underlying aetiology of disease [1].

## 2. Regulatory Mechanisms

The existence of a cell is regulated by a network of its molecular interactions. Cells can be reckoned as complex webs of macromolecular interactions, with a full complement constituting the "interactome" network [2]. The manner in which disease-related mutations contextually perturb protein functionalities in biological networks has been well-nigh impossible to decipher. Although, certain well-recognized alleles have been characterized, a paucity of data characterizes numerous disease-related variants. A vast majority of disease-associated alleles have demonstrated wild-type chaperone binding profiles which may preserve protein folding or stability. It is possible that variants in healthy persons minimally or rarely influence interactions, two-thirds of disease-associated alleles derange protein-protein interactions, with half correlating to "edgetic" alleles influencing merely a subset of interactions, without disturbing other interactions. In the presence of transcription factors, numerous alleles which do not perturb protein-protein interactions influence DNA binding. Varied mutations in the same gene resulting in distinct interaction profiles usually culminate in unique disease phenotypes. Therefore, disease-related alleles which impair distinct protein functionalities rather than expansively affecting folding or stability are more or less ubiquitous [3]. The significance of protein-protein interactions, and the ones between proteins and other macromolecules, such as nucleic acids, with the resultant specific complex production cannot be overemphasized. The potential of specific protein molecules to recognize their cognate associates and ligands in the congested in vivo ambient is crucial for the normal activity of the cell, providing the latitude for complex and inextricably linked life biochemistry to effectuate work. In the absence of protein-protein interactions, processes involving responses to signals, efficient and effective macromolecular syntheses and cell division may not likely take place. The output of intensive and expansive research is pertinent for the elucidation of protein structure and function, latitude for intervention in numerous pathological events, as well as infectious and neurodegenerative disorders, diabetes and carcinogenic perturbations. [4].

Gene regulatory networks, GRNs comprise physical and regulatory interactions among transcription factors, TFs and their DNA targets. As several disease-associated DNA mutations become identified in protein-coding regions of the human genome, there are extant expansive mutations in non-coding regions; thus suggesting that gene regulatory networks undergo alterations in human disorders. These could provide the framework for ardent analysis and mapping of human gene regulatory networks and enhanced throughput characterization of disease variants as well as develop interaction maps which constitute the networks regulating gene expression, and explicate genome mutations in human disease variants with potential regulatory roles for erstwhile unknown and newfangled approaches to understand specificities in human physiology as related to disease [3, 5, 6].

The Anfinsen concept relates that the one-dimensional primary poly-peptide sequence emphasizes the three-dimensional structure and, thus protein activity as a basic undergirding principle of modern biochemistry [7]. The DNA-encoded sequence translation into a faithfully folded polypeptide chain is relevant for cell vitality. In recent decades, molecular chaperones and associated enzymes are also involved in this critical activity. A slight breakdown in protein-folding control is liable to present debilitative impacts as depicted in deleterious neurodegenerative disorders, Morbus Alzheimer and Creutzfeld-Jakob disease. However, evidence abound that the primary structure is inadequate to explicate the three-dimensional configuration of the resultant protein product due to the thermodynamic energy profile of a folded protein depicting possible minima of low energetic barriers among them. Naturally, certain polypeptide sequences adopt alternative folding configurations with resultant distinct functional species. This is relevant for the functionality of a

single polypeptide in response to dynamic molecular ambient alterations. These responses are observed in protein interactions with representatives of the three main biological macromolecules, such as nucleic acids, proteins and lipid membranes. It is pertinent to elucidate the transition effects of the transitions of protein-lipid [8], protein-nucleic acid [9] and protein-protein [10] interactions in integrative cell biochemical, biological and biophysical instances [7].

Thus, transcription regulation is normally connected with expansive protein-protein interactions, especially for processes which are of benefit to the organism. In eukaryotes, for instance, a specific gene transcription usually results from detailed signal transduction pathways associated with protein modification, protein-protein interactions, and mobility between cellular compartments via positive and negative feedback loops which frequently culminate in an all-or-none response. The perspicuous engineering of transcriptional circuits is the main objective of synthetic biology [11]. Natural transcriptional regulation is dependent upon protein-protein interactions to enhance the regulated path that is not amenable in engineered systems. Mammalian signal transduction often proceeds due to interaction of a protein ligand with a cell-surface receptor resulting in phosphorylation on the cytoplasmic aspect of the cell surface culminating in alterations in protein-protein interactions which are invariably transmitted to the nucleus. Protein-protein interactions manifesting at the cell surface, in the cytoplasm and nucleus, and on the DNA generally depict latitude for engineering, and exhibit frequent thermodynamic problems [11] as detected in the viscosity of human blood plasma in the determination of health and disease [12].

## 3. System Biology/Bioenergetics

The objective of molecular system bioenergetics is a strategy to study intracellular interactions in energy metabolism regulation in healthy cells including their pathological manifestations. The paradigm of System Biology connotes complex biological system via the study of relatively non-dependent subsystems by describing their structure, function as well as the interactions between them [13]. Changes in intracellular structural interactions and production of mature energy metabolism in postnatal development constitute the model for the study of full and proper organized intracellular systems, in which the bioenergetic regulation of cell is distinct regarding structure. Variations in cell bioenergetics are pathognomic in the first instance of cell perturbation as cognizant in the bioenergetics of malignant cells. These make provision for the elucidation of bioenergetics of healthy muscle cells and cellular pathologies in ischaemia, myocardial infarction, cardiac failure, neurodegenerative diseases, bioenergetic mechanisms of malignant cells, and mechanisms of reperfusion derangement.

In the quantitative biophysical analysis of protein-protein interactions in health and disease with the application of data for rational drug design as fundamental, it is pertinent to explicate biological systems as they are influenced by disease as in cancer-associated cellular pathways or viral infection [14]. These include (i) analogues of protein-protein interactions in health to elucidate the workings of biological systems at the molecular level, (ii) elucidate the perturbations at the molecular level, (iii) drug research and development that will provide restorative potential to the biological system to healthy conditions, and inhibit untoward interactions, respectively in malignant cells and viral infections.

## 4. Trace elements

Mankind is dependent on certain trace elements, such as cobalt, copper, chromium, iodine, iron, manganese, molybdenum, selenium and zinc for optimum metabolic functionalities. These are involved in diverse regulatory and catalytic activities; and they interact with various macromolecules, such as enzymes, pro-hormones, presecretory granules and biological membranes [15].

The trace elements as micronutrients are invariably associated in all vital metabolic pathways, whereby their deficiencies are characteristically protean and non-specific. These elements are metabolically grouped as anions and cations as physicochemically characterized. The anions are absorbed relatively easily with entire body homeostasis being mediated principally via renal excretion. The cations have defined pathways for absorption with their homeostasis affected by biliary and gastrointestinal excretion. Certain trace elements are more efficiently absorbed as organic complexes. The overall objective in the metabolic pathways for each micronutrient is to a specific site of its functionality by engaging its physiochemical properties to preclude interactions with extraneous inorganic nutrients [15, 16]. These trace elements control vital biological processes when they bind to molecules on cell membrane receptor sites or by alternating membrane structure as to occlude ingress of specific molecules into cells. The dual significance of trace elements is exhibited respectively, in the normal stabilization of cellular structures and in deficiency conditions which may elicit alternate pathways culminating in disease [16].

## 5. Lysosomes

Lysosomes are at the fulcrum of the living cells with constitutive recycling functionality and ability for the digestion of exogenous material and endogenous organelles in the autophagy process. Dynamic interactions with other cellular components provide the lysosomal niche the convergence ambient in numerous diseases. Inborn lysosomal storage diseases are representative of circa 70 genetic variants with estimated cumulative birth frequency of 1 in 7500 [17]. Several of these are related to macromolecular storage resulting physical disruption of the organelle and cognate structures.

Ectopic dendritogenesis and axonal swelling resulting from distension with the membranous tubules and autophagic vacuoles are depicted in neurons. Deranged autophagy is ostensibly predominant in lysosomal disorders, but biochemical perturbation resulting from toxic metabolites, such as lysosphingolipid molecules, aberrant calcium homeostasis and reticulum stress responses as well as immune inflammatory processes manifest [17]. There has been no clear indication of the inextricable mechanistic linkage between isolated clinico-pathological manifestations and the underlying molecular impairment. Regarding the external fluid phase and intracellular trafficking pathways, the lysosome with its concomitant disorders have provided biotechnological interests, thus eliciting innovative orphan drugs as in the instance of Gaucher's disease, an effective regimen for haematological and visceral manifestations. As research indicates, two-thirds of lysosomal disorders present perturbing impacts in the nervous system. Thus, future therapeutic experimentation necessitates an integrative comprehension of the neuro-pathogenetic manifestations.

Genetic variants manifested by patients having primary defects in the lysosome present discrete perspectives regarding the

control function of lysosomes in human health and disease. It is important to realize that the inborn lysosomal disorders and their pathobiology, the cryptic evolutionary trajectories culminating in irreversible alterations need to be differentiated from the cellular storage phenotype as elucidated by the development of therapeutic gene transfer conducted at disparate site and distance manifestations [17].

## 6. Parkinson's disease

The pathological alterations which are observed in Parkinson's disease and numerous neuro-degenerative perturbations are complex and poorly elucidated; however, they are associated with protein aggregation with invariable concomitant mitochondrial aberration which ostensibly results from the same aetiologic factors from the same aetiologic factors or proximal interactions. The macroautophagy-lysosomal pathway is fundamental for the sustenance of protein and energy homeostasis. These are cumulatively manifested in the pathogenesis of Parkinson's disease in (a) the aggregation of deranged proteins and diminished cellular bioenergetics; (b) lysosomal impairment resulting in accelerated Parkinsonian perturbation; and (c) elicitation and augmentation of lysosomal functionality potentiates a disease modulation regimen [18].

## 7. Cystic fibrosis

Cystic fibrosis, CF constitutes a genetic disorder due to autosomal recessive mutations of the CF transmembrane regulator, CFTR with functionality in the epithelial cell membrane lining the epididymis, intestines, liver, lung, pancreas and the sweat duct. The fundamental issue in CF is that CTFR mutations affect its potential to be produced, processed and transported to the plasma membrane and/or its functionality as a $Cl^-$ channel and conductance regulator. Several proteins and processes usually interact with normal CFTR in its entire life cycle and mutant CFTR over time in the disease process [19].

## 8. Periodontitis

Periodontitis depicts as a chronic inflammatory disorder of tissue perturbation. In the deranged oral ambient, saliva fundamentally acts as a protectant via tissue lubrication, bone mineralization, pH neutralization, and microbial impact mitigation. In periodontal disease, there are alterations in numerous macromolecules, such as amino acids, carbohydrates, dipeptides, lipids and nucleotide metabolites with concomitant elevated macromolecular degeneration of glycerol-phospholipids, polysaccharides, polynucleotides, proteins and triglycerides in periodontal disease. There alterations ostensibly depict the augmented host-bacterial interactions in the diseased condition as revealed by elevated concentrations of bacteria-modified amino acids and creatine metabolite. Of increased significance is the accelerated glycosidase lipase and protease activities connected with periodontitis exacerbated by a disease condition favourable for oral bacteria [20].

## 9. Proteins

The manner in which disease-related mutations derange protein functions contextually in biological networks remains an enigma. Even though, certain alleles are expansively characterized, there is a paucity of functional data for an excess of 100,000 disease-related variants. A functional profile of inordinate number of missense mutations within a spectrum of Mendelian disorders employing diverse interaction assays reveal that a vast majority of disease-associated alleles depict wild-type chaperone binding profiles which suggest preservation of protein stability or folding [3]. Whereas, ubiquitous variants realized in healthy patients seldom effect interactions, it is clear that two-thirds of disease-associated alleles disturb protein-protein interactions, while half relating to "edgetic" alleles impact merely a minimal fraction of interactions, and no disturbing other interactions. On the aspect of transcription factors, several alleles which do not derange protein-protein interactions impact on DNA binding. Disparate mutations on the same gene resulting in discrete interaction profiles frequently culminate in unique disease phenotypes. In this regard, disease-associated alleles which disturb specific protein activities instead of expansively effecting folding and stability are relatively well-known [3].

Protein-misfolding disorders constitute perturbations due to misfolding of specific proteins which assemble and deposit in cells of mammalian tissues, albeit in an unclear manner. It is suggested that aberrant interactions between protein-misfolding disorder-associated proteins and nucleic acids can elicit conformational alterations observable in Alzheimer's, Parkinson's, prion diseases and transmissible spongiform encephalopathies [21]. The misfolding and aggregation of a specific protein as β-amyloid peptide for Alzheimer, α-synuclein for Parkinson's, and prion protein for transmissible spongiform encephalopathies are pathognomic for these diseases [22].

## 10. Biophysical and other Methods

The identification and characterization of cell macromolecular interactions are important to comprehend the underlying aetiology of disease. An expansive strategy has been employed to elucidate macromolecular structure, such as x-ray crystallography, NMR spectroscopy, and mass spectroscopy. The application of these and various biophysical methods, several researchers are involved in molecular interactions in an expansive range of human disorders [1].

Certain physical methods, such as sedimentation rate is used to investigate macromolecular interactions as a sophisticated technique that necessitates utmost precision in both experimental design and data analysis. Kinetic analysis of a vast array of macromolecular interactions with the evolution of experimental design and data analysis make adequate provision for accurate definition of the assembly mechanisms and rate constants conversant with macromolecular interactions [23].

Interactions among molecular species are central to all cellular processes, for instance, ligand recognition, catalysis and signal transduction. Thus, numerous diseases are inextricably linked to aberrant interactions between coupled molecules. This necessitates design, research and drug development capable of reversing such perturbations ([23, 24]. There are extant studies on molecular interactions on the application of combined biophysical, biochemical, and molecular genetics and live-imaging strategies: A model system comprises the bacterial toxin, adenylate cyclase from Bordetella pertussis that is an aetiological agent for whooping cough. Rudimentary information and knowledge on the mechanisms of toxin ingress into the eukaryotic target cells coupled with its interaction with cellular effectors are employed in vaccinology and biotechnology [25].

## 11. Discussion and Conclusion

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 morphological configuration and functionality of macromolecules are designed whereby several disorders are directly related to aberrant interactions between molecular pairs which provide the latitude for drug designs capable of reversing untoward biological features [23]. Also, concomitant tracking of transient organelle communities and interactions necessitates effective and efficient real time dynamics and analysis in viable living cells via the application of multi-colour fluorescent probes. Numerous fluorescent proteins utilized for live-imaging are limited by the oxidizing ambient of several organelles, such as endoplasmic reticulum, golgi complex or apparatus, and secondary vesicles. It is pertinent to elucidate protein complexes which relate and modulate newfangled organelle communities via the application of cooperatively new technologies in mass spectrometry coupled with fluorescent protein-based probes for live cell imaging. Interorganelle interactions constitute vital processes regulating eukaryotic cell function; and dysregulation of these interactions is culpable in numerous human disorders. There is paucity of data on the macromolecular complexes which mediate organelle interactions because numerous important proteins are integral membrane proteins which ostensibly defy purification with sustained physiologically labile but relevant binding interactions. These interactions are not easily amenable to conventional biochemical and genetic strategies [26].

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