Review Article

Intrinsically Disordered Proteins, Structural and Functional Dynamics

Irum Naureen[1], Aisha Saleem[2*], Hafiza Hira Rehman[2], Umar farooq[2], Iqra Iqbal[2], Tayyaba Sehar[2], Tahir Ali[2]

[1]Assistant Professor, School of Zoology, Minhaj University Lahore, Pakistan
[2]M. Phil Researcher, School of Zoology, Minhaj University Lahore, Pakistan

*Corresponding author: Aisha Saleem
M. Phil Researcher, School of Zoology, Minhaj University Lahore, Pakistan

Abstract

The classical theory is that before being biologically active, proteins are assembled into a unique three-dimensional structure in terms of quality. These Intrinsically Disordered Proteins (IDPs) are very common in many genomes, including humans and play a key role in central cell processes such as transcription and translation, cell cycle, and cell signaling regulation. In addition, the proportion of proteins associated with various diseases such as cancer and neurodegenerative diseases is very high in IDPs. Therefore, considerable efforts have been made to elucidate the molecular mechanisms supporting the role of IDPs in Biology and disease through the use of experimental and computational methods. Animal models are needed for human genetic anatomy and better treatment options. Genetic disease Although some animals are used key models in academic and industrial research .There is a lot of stress in the anatomy of genetic diseases. The Genetic resemblance of rats and the humans from which is naturally occurring genetic disease, unique population. The availability of structure and complete genomic sequencing has made purebred dogs a powerful model. Used for disease research. The main advantage of dogs is that they suffer from about 450 genetic diseases, of which about half show significant medical symptoms, Similar to the same human disease. Therefore, these two facts make dogs an ideal medical practice, and a genetic model. This review sheds light on some of them, common genetic disease, in dog model. In this article plays an important role in identifying the genes responsible for the disease and / or the use of new genes, treatment of interest for dogs and humans.

Keywords: Disordered proteins, Regulated unfolding, Muscular dystrophy.

INTRODUCTION

After synthesis on the ribosome, most proteins are arranged in a unique three-dimensional structure, determined by the sequence of amino acids. This folding process is usually required for biological activity, whether it is artificial or with the help of molecular chaperone [1]. However, proteins studied at the molecular level are increasingly unrelated to the function of a single structure [2, 4]. In contrast, for this type of so-called Intrinsically Disordered Protein (IDP), the greatest feature of the natural state is the dynamic set of inter conversion conformation.

In this case, the term "error" means lack of some stable three-dimensional structure. Many other terms, such as "unstructured" and "expanded" are also widely used to describe this phenomenon, but the name IDP is currently the most widely used for this type of protein. IDP structural disorders can occur in one or more separate areas along the strand, or they can spread over the entire length of the protein. The concept of defects in protein structure is not really new. For example, the peptide hormone [5] the "linker" that binds to the domains of a multi-domain protein, or the loop that binds to the secondary structural elements of other configured proteins, may have large amounts of structural heterogeneity [6].

There is X-ray crystallography experiments usually have gaps in the electron density map [7]. However, over the past decade, with the development of protein biophysical characterization techniques, particularly nuclear magnetic resonance (NMR) spectroscopy [8] and bioinformatics tools to predict disease directly from amino acid sequencing, it has two broad effects [9]. It is clear that protein deficiency is very common in many organisms, especially in complex organisms. In the bacterial genome, it is estimated that only 4% of all proteins contain chaotic regions that are at least 30 amino acids long, while the

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same number of eukaryotes is about one-third [10], but in the case of humans. In, it's about half [11].

Protein abnormalities have been shown to play an important role in many central cellular processes. For example, IDP is shown as a signal hub for protein-protein interaction networks [12, 13]. The part of the nuclear pores, transport lipids and cholesterol in the plasma [14], produce membrane-free organelles in the cytoplasm and nucleus [15]. Subsequent mutations in RNA regulate cell cycle development [18]. The spread of the disease varies widely among the different functional classes of proteins. For example, proteins with catalytic cell function are predicted to be less degraded than proteins with regulatory function [11, 12]. This biased distribution reflects a significant role of impairment in certain functional molecular mechanisms. [16] This is the traditional approach to enzymes; as the molecule relies on a strong structural framework (with significant but secondary kinetic behavior) to accurately locate important residues at the catalytic site [17].

The enzyme has structural damage and is related to a wide range of properties of the substrate [19]. Due to its broad regulatory role, IDPs are slightly contradictory and are usually involved in protein binding and molecular recognition [20]. To identify a particular partner molecule, IDPs typically go through a chaos when they are in contact with a target. This binding folding and binding process is one of the many functional benefits that IDPs provide for ordered proteins. One such advantage is that IDP can combine structurally different things [21].

For example, the primarily chaotic GTPase binding domain of Wiskott - Aldrich syndrome Protein (WASP) binds to its VCA domain, which in turn blocks itself and binds GTPase Cdc42 in various ways. This structure triggers WASP activation and actin polymerization [22]. Another example is the primarily dysfunctional C-terminal region of the tumor-suppressing , which may be associated with at least four different configured proteins, sirtuins, cyclins A2, transcription co activators CBP (CREB binding protein) and S100B growth [23]. This review article describes some of the molecular mechanisms behind IDP functionality. The field of IDP research has grown rapidly over the last few years and is now very large. There are several excellent reviews discussing the broader role of IDPs in biology (e.g. Dunkir *et al*., [2]. Wright and Dyson [3], and Habchi *et al*., [4]. The review focuses on four new areas where IDPs have recently been identified to play a key role: allosteric, regulatory development, formation of membrane-free organelles, and physical complexes. In addition, it's potential as an IDP and its interaction as a treatment target.

Hemophilia B

Hemophilia B is caused by a mutation in the factor IX (FIX) gene on the X chromosome. FIX is synthesized by hepatocytes and is an important part of the clot. Lack of clotting factors can cause bleeding in the joints, soft tissues and muscles. This bleeding may be spontaneous or it may be due to a minor injury [23]. It is estimated that 1 in 30,000 men develop hemophilia B, which is medically and molecularly contradictory. About 1,000 unique mutations that cause hemophilia B have been reported in humans [24]. Hemophilia B in dogs is very similar to human disease and is well studied [25]. Published FIX Code Setting for Dogs. The same team also identified the first known mutation that causes hemophilia B in dogs. This is a misconception that results in no identifiable protein [26]. Since then, numerous cases of different types have been reported and five different mutations have been reported

Table 1: Mutations in canine hemophilia B

BREED	MUTATION	REFERENCE
Notreported	Missense	**[25]**
LhasoApso	5-bpdeletion	**[30]**
LabradorRetriever	Completegenedeletion	**[27]**
AmericanPitBullTerriermix	Partialgenedeletion	**[29]**
AiredaleTerrier	5-kbinsertion	**[29]**
GermanWirehairPointer	LINE1insertion	**[28]**

The standard treatment for hemophilia B is intravenous infusion of FIX concentrate to prevent or treat bleeding. Treatment is effective and generally safe, but expensive and painful [31]. Molecular therapy for hemophilia B is being studied not only to provide patients with treatment options, but also to evaluate the overall effectiveness of such methods. The factors that make hemophilia a good model for evaluating genetic intervention strategies are (1) the need for tissue-specific gene expression, and (2) A significant phenotypic increase in clotting factor levels. Improves, and (3) clotting factors. Surface measurements can be obtained from a simple blood test and (4) a naturally occurring dog model can be used .Due to a misunderstanding, the group of dogs with hemophilia B is Evans et al. Characterized by the first. It has been used in many important gene therapy studies [31, 32]. A retroviral vector containing FIX cDNA was first used as a result of low-level long-term expression of FIX [33].

Subsequent studies used recombinant adenovirus vectors to obtain short-term expression of FIX at treatment levels. [33] To achieve the long-term and therapeutic level of FIX expression in thesedogs, researchers have successfully used the adeno-associated virus (AAV) vector [34]. The AAV vector was then used to correct severe hemophilia B phenotype in dogs with a mutation [36]. The data obtained using AAV vectors in the study of these dogs provide evidence of the principles needed to advance the trial of human hemophilia B gene therapy [37]. Dogs also played a key role in advancing molecular therapy for Haemophilia A due to a deficiency of factor VIII [31]. Haemophilia A is much more common than Haemophilia B, but research into gene therapy has been hampered by large FVIII genes [38].

Muscular Dystrophy

The most common and serious muscular dystrophy in humans is Duchenne Muscular dystrophy (DMD). DMD is an X-ray disease that causes muscle degeneration and death at about age 20. 1 in 3,500 men is affected and there is currently no effective treatment. Naturally occurring DMDs have been described in Golden Retrievers [39]. Golden Retriever Muscular Dystrophy (GRMD) is characterized by increased activity of serum creatine kinase, progressive muscular atrophy and necrosis, and regeneration of fibrosis and adipose tissue. Infected dogs show clinical symptoms within 8-10 weeks [40]. DMD is caused by a defect in the dystrophin gene, which encodes a cytoskeletal protein involved in fascial stabilization [41].

Northern and Western blots using human probes failed to detect dystrophin transcripts or proteins in GRMD-affected dog muscle tissue [42]. Sequence analysis of the dystrophin gene revealed a transition from A to G in exon 7 splice acceptors in affected dogs [43]. This mutation either removes exons 7 or uses alternative splicing sites 5 bp downstream. In both cases, the reading frame is shifted and the transcript is truncated [44]. The frequency and severity of DMDs have stimulated a patient's interest in developing gene therapy.

Although significant advances have been made in the mouse model, the more similar the disease progression, the more attractive the dog becomes [45, 46]. The first gene therapy studies in dogs focused on the dystrophin gene and were very promising [47]. Another approach involves upregulation of eutrophin, a gene that is similar in function and structure to dystrophin but is not extrinsic in DMD patients [48]. Delivery of the mini-eutrophin transcript via the adenovirus vector reduced the dystrophy phenotype of GRMD canine muscle, but a slight immune response occurred between the vector and the transgene.

Another method involves modified antisense oligonucleotides (AOs) that cause exon skipping. By modifying the splicing pattern, AO can remove the mutated exons from the precursor mRNA, resulting in a functional protein [49]. McClowry was successfully used to restore dystrophin expression in dogs. Studies of gene therapy in humans have also been successful, with several types of carriers being used to deliver dystrophin to the dystrophin muscle. AAV vectors are problematic due to their limited carrying capacity and the large size of the dystrophin gene. The use of microdystrophin, a shortened but functional version of the dystrophin gene, is promising and preliminary studies are underway [50].

In addition, with the success of AO treatment in dogs, Phase 1 human clinical trials have begun To eliminate in response to the immune response of the carrier and / or the dystrophin gene itself, researchers have studied the use of stem cells to treat GRMD. A mouse mdx model has shown that hematopoietic stem cells are effective in muscle regeneration [50] unfortunately, normal littermate hematopoietic stem cells do not cause muscle regeneration in affected dogs. Blood vessel-related stem cells called mesangioblasts are also being studied [50]. Mesenchymal hemangioblasts were successfully transplanted and expressed dystrophin, thereby restoring muscle use [51]. Wild-type donor hemangioblasts have been found to be more effective than genetically modified autologous hemangioblasts. All dogs treated with wild-type cells showed early improvement in mobility, and one dog walked for 5 months after discontinuation of treatment.

Regulatedunfolding

Recent studies have revealed new cellular regulatory mechanisms that rely on the development of dynamic protein structures from signals such as ligand binding, mechanical stress, post-translational modifications, and pH changes. Different stages of development have been observed from the local development of secondary structural elements to the overall development of the whole protein [52]. An example of a regulation opened by ligand regulation is found in the mitochondrial pathways of programmed cell death [53]. Which suppresses tumors, binds to various pro-apoptotic proteins (such as BAX) to stimulate apoptosis, leading to permeability of the outer mitochondrial membrane and consequent cell death.

However, the apoptotic function is usually inhibited by the isolation of cytoplasmic in inactive complexes formed with the anti-apoptotic protein Bcl-xL [53]. This separation is controlled by PUMA's unique chaotic BH3 domain, where p53 upgrades the apoptotic regulator. It binds to Bcl-xL and in the process merges into a single α-helix. Interestingly, the combination of PUMA and Bcl-xL also caused local expansion of the two α-helixes of Bcl-xL, α2 and α3, breaking the Bcl-xL coupling interface [54].

In particular, the correct method of elastic coupling observed in KIX has been widely discussed in the literature in terms of experiment and theory [58, 59]. One of the binding partners of KIX, c-Myb, is a simulation factor involved in the differentiation and proliferation hematopoietic cells of.
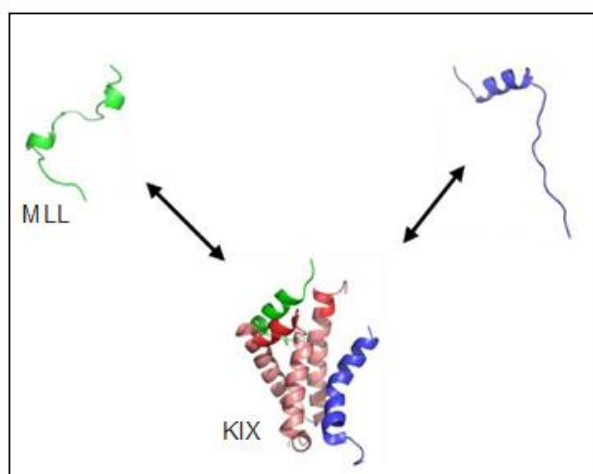

Figure 2: The central Trans activation domain of C-Myb itself is chaotic, but once connected to KIX, it collapses into a single twisted α-helix [56, 57]

The KIX domain (salmon and red) of CBP can simultaneously bind the two ligands c-Myb (blue) and MK (green). In isolaton both ligands lack a stables structure. Circular dichroism measurements show cMy to be 30% helicle [59]. Association with KIX, both cMyb and MLL fold into stable- helical structures, but binding occurs to different binding's sites in KIX. [60] Performed a molecular dynamics simulation of interaction between selected regions of c-Myc and related compounds.

Fragmentation of the simulated c-Myc differed in the two computational studies, but similar interaction sketches were obtained. First, ligand 10074-A4 does not induce the integration of c-Myc into specific structures such as Max. This corresponds to the circular decrom data. In contrast, the configuration set of the monomer c-Myc is only slightly disturbed by the ligand. The 10074-A4 binds to multiple points in the c-Myc chain, forming a "Legend Cloud" around the IDP confirmation; there is no single dominant binding mode [54, 58].
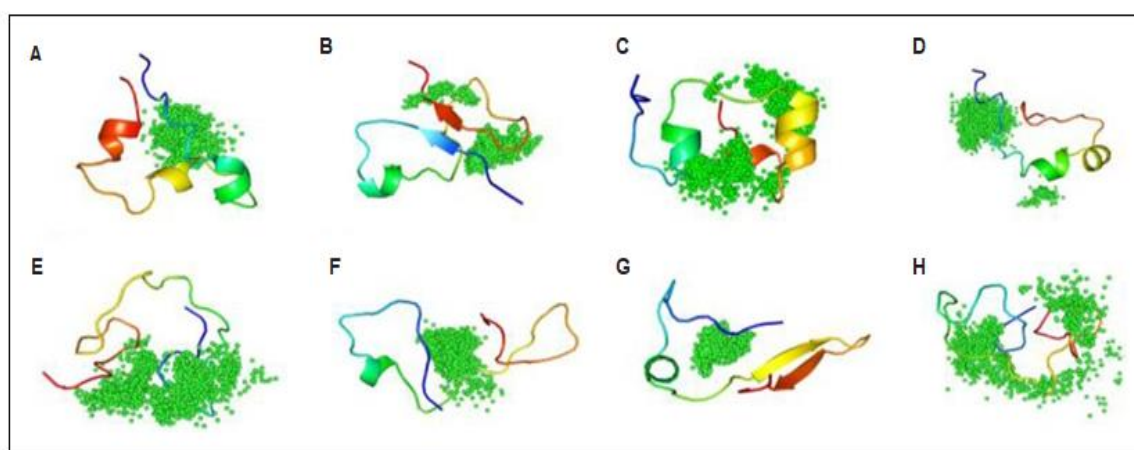

Figure 3: ligand cloud around a protein cloud. (A–H) Interaction between the region of c-Myc and the ligand 10074-A4 (green), as represented by the eight most populated structures of c-Myc obtained from a cluster analysis and the center-of-mass points of the ligand [59]

CONCLUSION

Human resource development was completed after research on the IDP development system in the 1990s. Minor effort remarks, very universal in IDP licensed multifactorial group, minor growth cell processes, and non-transmissible dyskinesia during normal processes. Cell Regulator Significant Emerging Area, Composite Structure, Even Regulatory Development Japanese Membrane Cell Processing Body Formation Individual Biology, Universal Japanese Basic Process, IDP, Human Disease, Common and Positive Effort, Modern Treatment of IDP, Disease

Due to Unemployment. Genetic disorders that affect humans and dogs, in dogs and humans, the genetics of complex diseases are more difficult to determine. However, with the new genomic tools / resources available for dog research, staff are now beginning to analyze complex diseases. Such as cancer, heart disease (such as cardiomyopathy), and neurological disorders (such as epilepsy). Dogs and human behavior, morphology, and other factors influencing disease progression may be the same, but the major genes that affect them may be the same.10074-A4. First, ligand 10074-A4 does not induce the integration of c-Myc into specific structures such as Max. The 10074-A4 binds to multiple points in the c-Myc chain, forming a "Legend Cloud" and there is no single dominant binding mode.

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