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Featured Article

Minimotifs dysfunction is pervasive in neurodegenerative disorders

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Abstract Minimotifs are modular contiguous peptide sequences in proteins that are important for posttranslational modifications, binding to other molecules, and trafficking to specific subcellular compartments. Some molecular functions of proteins in cellular pathways can be predicted from minimotif consensus sequences identified through experimentation. While a role for minimotifs in regulating signal transduction and gene regulation during disease pathogenesis (such as infectious diseases and cancer) is established, the therapeutic use of minimotif mimetic drugs is limited. In this review, we discuss a general theme identifying a pervasive role of minimotifs in the pathomechanism of neurodegenerative diseases. Beyond their longstanding history in the genetics of familial neurodegeneration, minimotifs are also major players in neurotoxic protein aggregation, aberrant protein trafficking, and epigenetic regulation. Generalizing the importance of minimotifs in neurodegenerative diseases offers a new perspective for the future study of neurodegenerative mechanisms and the investigation of new therapeutics.

Keywords: Minimotif; Posttranslational modification; Trafficking; Binding; Aggregate; Epigenetics; Genetics; Histone code; GWAS

1. Introduction

Minimotifs, also called short linear motifs, are short contiguous peptide sequences or sequence patterns that encode molecular functions. These functions range from the binding of a protein to other proteins and molecules, posttranslational modification (PTM) of a protein, or trafficking of a protein to a subcellular compartment. Two main minimotif databases, Minimotif Miner and the Eukaryotic Linear Motif resource, now house more than one million minimotif instances [1–6]. Recent proteome-wide analysis of minimotifs with 1000 genomes data determined that the vast majority of minimotifs are fixed in humans, suggesting their importance in cellular function [7,8]. At the fundamental level, each minimotif is defined as a sequence or sequence pattern in a source protein and an activity that connects the motif to a target protein. The target protein can be an enzyme for PTM, an interaction with another molecule such as a protein, or a trafficking receptor.

The conservation of most minimotifs and their role in evolution suggests that they might render a significant vulnerability to diseases [5,7–9]. In the first comprehensive review of minimotifs in human diseases in 2007, our group noticed that minimotifs were involved in disease, particularly infectious diseases, and others have expanded on this observation [5,9,10]. There are at least 35 minimotifs mutated in more than 20 diseases, including both rare and common disorders [11]. These include the three

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general classes; binding, PTMs, and trafficking minimotifs. Several annotations for diseases are listed and described on the Eukaryotic Linear Motif resources website. Approximately 0.1% of missense mutations in the COSMIC somatic cancer mutation database overlap with a minimotif. There are 100s of minimotifs encoded by viruses that are used to hijack host cell processes, several essential for the viral life cycle.

Another line of evidence for the importance of minimotifs in disease is the emergence of Food and Drug Administration (FDA)-approved minimotif mimetic drug therapeutics [11]. For example, protein kinase inhibitor drugs such as Gleevec (imatinib mesylate), Iressa (gefitinib), Sprycel (dasatinib), and Stutnet (sunitinib) among others block phosphorylation of minimotifs and have become useful for cancer treatment and immunosuppression [12]. Drugs that block different proteases that cleave minimotifs such as Lotensin (benazepril), Novastan (argatroban), Januvia (sitagliptin), and many HIV protease inhibitors are also minimotif-directed therapeutics. Peptide hormones tend to have core clusters of amino acids that bind to receptors. For example, peptide therapeutics or chemical agonists such as Supprelin LA (histrelin) for the Gonadotropin Releasing Hormone receptor, Byetta (exenatide) for the glucagon-like peptide 1 receptor, Somatuline Depot (lanreotide) for the somatostatin receptors, and opiates such as Demerol (meperidine) for opioid receptors mimic the determinants of this core cluster in interaction with receptors. There are also antiviral drugs to several lipidation enzymes that modify minimotifs, and tirofiban is a drug that mimics the Arg-Gly-Asp ligand for integrins.

In this review, by exploring the specific role of minimotifs in NDs, we consolidate significant evidence that supports our hypothesis that minimotifs have distinct and generalizable functional roles in ND etiology. Minimotifs are the key connections in the cellular molecular network, so it is not surprising that they are vulnerable to pathological dysfunction and that all NDs have multiple dysfunctions of minimotifs. By questioning whether the modification of minimotifs is causal or a consequence of other precipitating events, we recognize both are contributing factors to NDs. From the causal perspective, some of the familial genes in NDs have mutations that disrupt minimotifs or minimotif targets. Minimotifs may also be causal through PTM of the histone code and epigenetics. Other, less direct roles of minimotifs in pathogenesis are through protein trafficking, PTMs, neurotoxic protein aggregation, and aggregate clearance.

Because there are approximately 100 NDs known [13], in this review, we have focused on only the major NDs: Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and tauopathies, although where relevant, other NDs are mentioned.

2. Types of minimotifs in neurodegenerative diseases

All three types of minimotifs: binding, modifying, and trafficking, have important roles in neurotoxic aggregate formation and clearance, epigenetics through the histone code, protein trafficking, and PTMs of ND-related proteins. Some of the genes with familial inheritance in NDs harbor mutation in minimotifs or enzymes that modify minimotifs, as summarized in Tables 1 and 2 and discussed below.

2.1. PTM minimotifs in neurodegenerative diseases

Previous reviews of NDs summarize the important roles of PTMs, one general category of minimotifs. There are more than 500 types of covalent modifications, with most, if not all proteins in the human proteome having one or more modifications [14]. These PTMs perturb local and global structural changes thereby altering protein binding, trafficking, half-lives, activities, and signaling. Therefore, it is not surprising that several of these modifications have substantial roles in the pathology of NDs.

2.1.1. Glycosylation/glycation

Half of all proteins in most cell types undergo glycosylation and are N-glycosylated at the minimal consensus sequence Nx [S/T] and/or O-glycosylated on Ser or Thr with no specific sequence determinants [15–17]. Protein glycosylation stabilizes protein structural folds and facilitates protein trafficking, protein quality control, receptor activation, and endocytosis [17,18]. Human mutations in N-glycosylation sites can result in severe disease pathology; for example, a familial T183A mutation in a NxT glycosylation minimotif in a prion protein (PrP) can result in Creutzfeldt-Jakob disease (CJD) [11,19–22].

Curiously, there are also several germline mutations immediately juxtaposed to a N-glycosylation consensus sequence: a P504L mutation in WFS1 of Wolframs syndrome, E196K, V180I in PRP for CJD (P04156), and E196K also in Gerstmann-Straussler disease [23–25]. However, whether these mutations alter glycosylation and influence pathogenesis is not yet clear.

Also unclear is the observation of altered glycosylation in NDs, a likely downstream event or epiphenomena. On a global scale, proteomic analyses of AD brains identified 131 GlcNacylation sites in 81 proteins that revealed altered glycosylation. Another global study on the brain and sera isolated from the HD transgenic mice identified differences in the amount and the pattern of glycans in mice showing pathology [26]. Aberrant glycosylation of an additional ten glycosylated proteins in NDs (AD, PD, and HD) was summarized previously [27]. Acetylcholinesterase is abnormally glycosylated in both CJD and AD [27,28]. Nonenzymatic glycation and aberrant glycosylation of tau are prevalent in AD and FTD [29–32].

2.1.2. Phosphorylation

Protein phosphorylation of Ser, Thr, or Tyr residues is biologically significant throughout development of disease. During the pathogenesis of NDs, aberrant phosphorylation results in the misfolding and aggregation of neurotoxic