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Post translational Modifications and Protein-Protein Interactome of Endemic Pemphigus in El Bagre, Colombia: A New Variant Analysis

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ABSTRACT

Introduction: A new variant of endemic pemphigus foliaceus, El Bagre-EPF, is an orphan autoimmune disease occurring in El Bagre and neighboring municipalities in Colombia, South America.

Objectives: We aimed to evaluate current state-of-the-art databases and protein-protein interactomes, focusing on post-translational modifications as potential tools to study interactions among El Bagre-EPF antigen proteins.

Methods: We consulted multiple databases for the known target antigens and their protein-protein interactions. We searched for their network nodes (they represent proteins; each node corresponded to all the proteins produced by a single, protein-coding gene locus). We also searched for any post-translational modifications.

Results: We identified similarities in proteins bound by several autoantigens but also found differences in protein linkages. We found that desmoglein, periplakin, desmoplakins, and proteins from subfamilies of the Armadillo repeat proteins and some spectrin domains linked to other cell junctions; these played important roles in membrane-plaque and intermediate filament junctions. A typical drawback in current databases is the lack of information on lipid-protein interactions.

Conclusions: Our results show that state-of-the-art protein databases as tools for studies of interactomes fall short in areas including tertiary and quaternary protein interactions and in vivo protein functioning. Enhanced three-dimensional or multi-dimensional functions are required for more accurate interactome analyses.

Introduction

A new variant of endemic pemphigus foliaceus (El Bagre EPF) is an autoimmune disease occurring in El Bagre, Colombia and surrounding areas [1]. An interactome documents a wide range of binding interfaces with varying degrees of flexibility, from rigid globular domains to disordered regions that lack native structure. Protein-protein interactions are classically studied using methods including co-immunoprecipitation (CO-IP) and yeast two-hybrid systems [2]. A proteome-scale map of protein-protein interactions was reported with COVID-19 [3].

Objectives

Here we aimed to evaluate current state-of-the-art databases detailing protein-protein interactomes of the El Bagre-EPF antigens in humans [4].

Methods

We consulted network nodes, which link to all the proteins involved in direct interactions. We accessed UniProt, [5,6] and Research Collaboratory for Structural Bioinformatics PDB [7, 8] including three dimensional (3D) structures as well as ConsensusPathDB-human [7-9], STRING [10,11], and PhosphoSitePlus® [12,13], which document protein post-translational modifications (PTMs) including phosphorylation, glycosylation, and acetylation [12,13]. We also retrieved information from the National Library of Medicine [14] and NextPro [15]. All databases were reviewed in May 2024.

Results

Desmoglein-1 (Dsg1)

UniProt name Q02413, Dsg1 protein has 1,049 amino acids (aa) and a mass in Daltons (DA) of 113,748. Dsg1 is a type I membrane glycoprotein of the cadherin family. The Dsg1 ectodomain contains 29 aa and includes four cadherin repeat domains and globular motifs. The mature form of Dsg1 forms a homodimer, joining molecules at the cell surface via cysteine residues. The cytoplasmic tail of Dsg1 interacts with intermediate filaments (IF) including desmin in the heart and keratin in the skin via plakoglobin. Dsg1 has one Caspase (CS) -3 and one CS-7 cleavage at sites 885-889 in its alpha chain, in both the nucleus and cytoplasmic sites. Dsg1 is an antigen for pemphigus foliaceus (PF), Brazilian endemic pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris (PV), and El Bagre EPF. Dsg1, found within desmosomes and interacts with plaque proteins, has calcium and other metal binding sites. Mutations in Dsg1 are associated with severe dermatitis, multiple allergies, and metabolic wasting syndrome (MWS).

In Figure 1, we present primary (A), secondary (B), and tertiary (C) Dsg1 network nodes, and in (D), 3163 physical nodes. The first node includes desmocollin-1 (DSC1) and desmoplakin (DSP), the second node includes DSC1, DSP, corneodesmosin (CDSN), plakophilin-1 (PKP1), and junction plakoglobin (JUP), also known as plakoglobin. The third and additional nodes include plakophilin-2 (PKP2), filaggrin (FLG), plakophilin-3 (PKP3), desmocollin-3 (DSC3), and periplakin (PPL).

In Supplementary File 1, we show Dsg1, DSP, envoplakin, and PPL nodes containing at least 144 nodes and 3163 physical protein interactions. The main Dsg1 interaction is between plakoglobin and the catenin complex gamma subunit. Dsg1 PTM includes the cleavage on at least one pair of basic residues. Dsg1 is both a glycoprotein and phosphoprotein. Dsg1 has two isoforms (IS): Q02413-1 (Dsg1), which is the canonical sequence, and Q02413-2(Dsg1 IS 2), featuring 408 aa and 42,619 Da. Mutations of Dsg1 cause palmoplantar keratoderma 1 (striate, focal, or diffuse), and transmutations of Dsg1 cause congenital erythroderma with palmoplantar keratoderma, hypotrichosis, and hyper IgE. The Dsg1 taxonomy is GO:0101003, and Dsg1 also has a ficolin-1-rich granule membrane.

Envoplakin (EVPL)

UniProt name Q92817, 2033 aa and 210 kDa is a cornified envelope precursor protein and represents the paraneoplastic pemphigus antigen (PNP) p210. EVPL is a component of the cornified cell envelope (CCE) of keratinocytes in the skin and may link the CCE to the desmosomes and the IF. EVPL plays a role in the regulation of antibacterial peptide production. EVPL participates in peptide cross-linking and in keratinocyte differentiation. EVPL assists in IF cytoskeleton organization, epidermis development, wound healing, and extracellular exosome generation. EVPL has spectrin and plectin domains. As with Dsg1, EVPL has C-3 and C-7 cleavage sites in both the cytosol and nucleus. EVPL has two IS, one of which may form a homodimer or a heterodimer with PPL. The EVPL network contains 77 interaction nodes and 476 physical entity nodes. In Figure 2, we present EVPL primary, secondary, and additional interactions.

Desmoplakin (DSP)

UniProt name P15924; 2,871 aa and 331,774 Da. DSP, integral to desmosomes, regulates profibrotic gene expression in cardiomyocytes via activation of the MAPK14/p38 MAPK signaling cascade and grows in TGFB1 protein profusion.

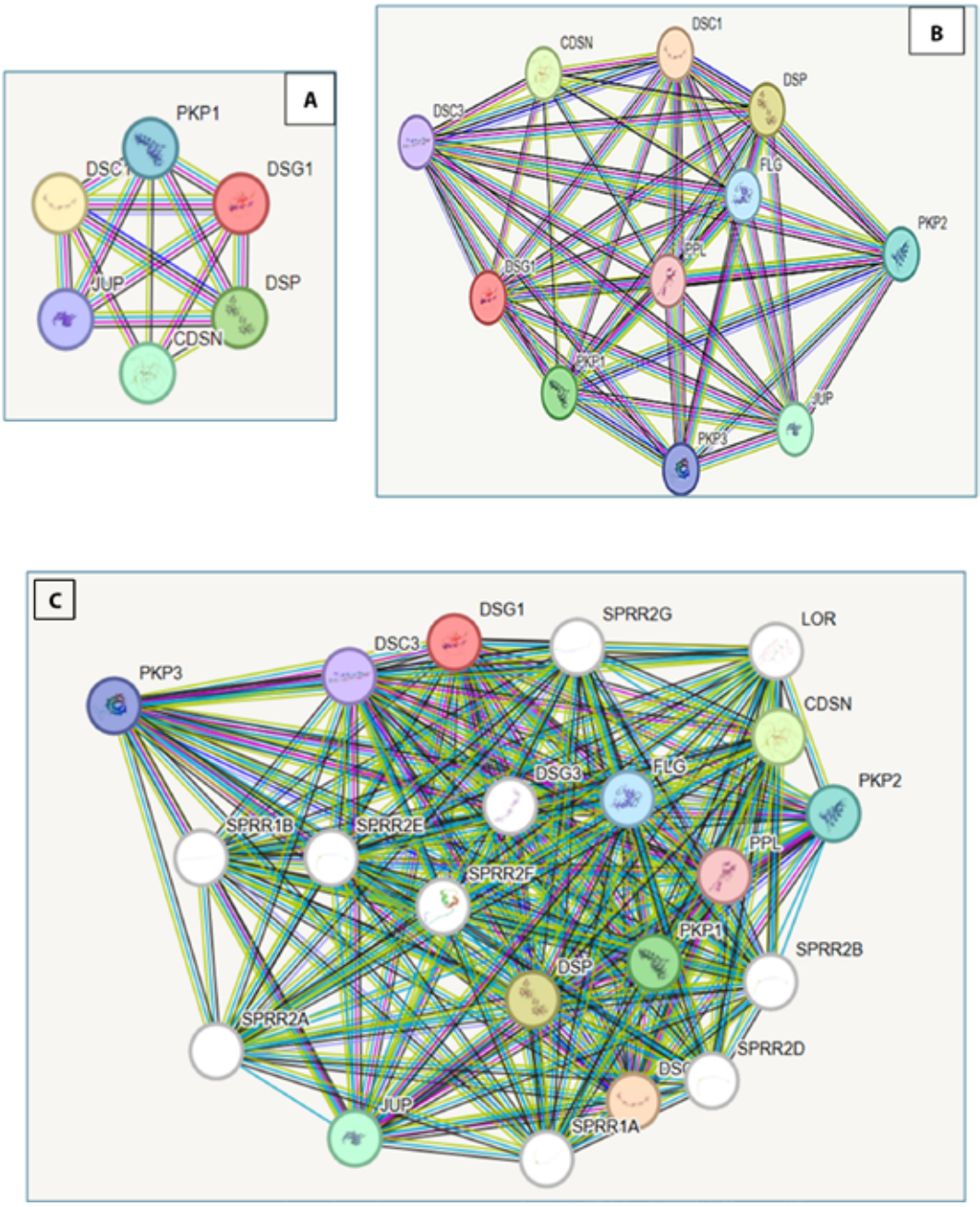

Figure 1. Desmoglein 1. (A) Primary interacting node. (B) and (C) Secondary and tertiary interacting proteins. Credits: https://string-db.org/cgi/network?taskId=bTUttl7D3iAn&sessionId=bds886FqwOhw

DSP has three IS: DSP1 (P15924-1), DSP2 (P15924-2), and DSP3 (P15924-3). DSP is part of extracellular exosomes. As with epiplakin, DSP has spectrin and plakin domains. DSP has a link to adherens junctions (AJ) and is part of cell-cell junctions with N-cadherin. DSP is also part of intercalated disc structures and part of the CCE. The PTM of DSP includes methylation and phosphorylation. DSP has one C-3 and C-7 cleavage in both the nucleus and cytoplasmic sites. DSP is part of the attachment of the bundle of His cells to the Purkinje myocytes via adhesion molecules and thus affects cell communications. As with Dsg1, DSP also has a ficolin-1-rich granule membrane; its lipid bilayer surrounds the ficolin-1-rich granule. DSP is a scaffolding protein, with roles in signaling pathways and has spectrin and plakin domains, similar to envoplakin; DSP also binds to RNA as well as to protein kinase C. DSP exhibits a nuclear location.

In Supplementary File 1, we present the interacting nodes for Dsg1 containing 144 interaction nodes and 3163 physical entity nodes. The Dsg1 primary interaction is with JUP/plakoglobin. Dsg1 also binds to the catenin complex gamma subunit. DSP interacts with desmogleins 1 and 2, DSC1 and 2, PKP1 and PKP2, Cytokeratin 8, PPL, envoplakin,

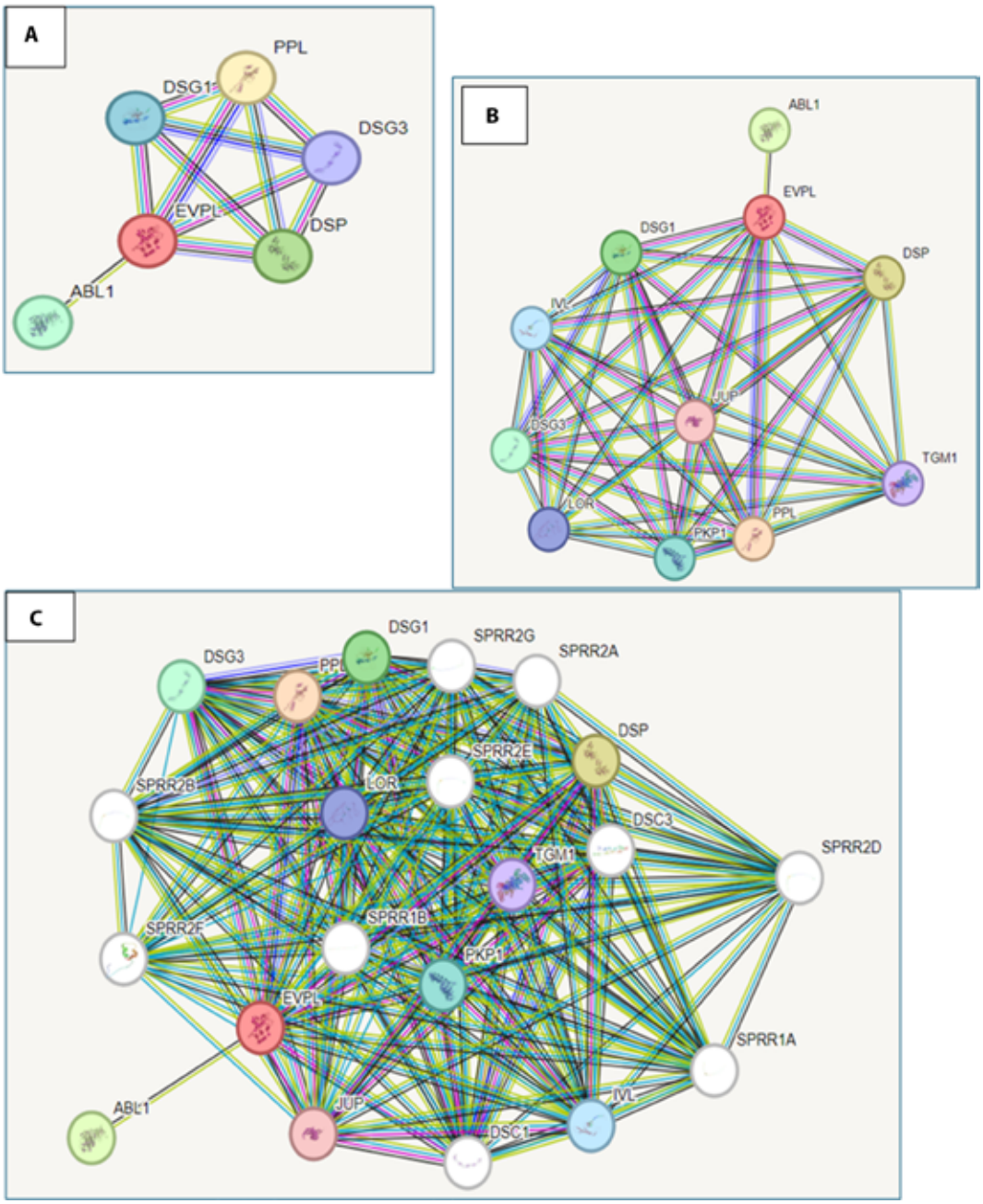

Figure 2. Interaction nodes for envoplakin.
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and plakoglobin. The DSP network contains 262 interaction nodes and 575 physical entity nodes. In Figure 3 and in Supplementary File 1, we show DSP 3D nodes. DSP mutations are associated with Carvajal/Naxos syndrome, associated with leukonychia, oligodontia, tooth agenesis, keratoderma, the striate subtype of palmoplantar keratoderma, cardiomyopathy, arrhythmogenic right ventricular dysplasia, arrhythmogenic right ventricular cardiomyopathy, skin fragility-woolly hair syndrome, and epidermolysis bullosa.

Periplakin (PPL)

UniProt name O60437, 1756 aa. The PPL protein is a component of the CCE of keratinocytes. PPL may link the cornified envelope to desmosomes and the IF. PPL seems to participate in protein kinase PKB/AKT-mediated signaling. PPL interacts with kazrin and butyrophilin (BTN) BTN3A1. The BTN subfamily 3 member A1 plays a role in T cell activation and in the adaptive immune response including proliferation of activated T cells, release of cytokines, and interferon gamma by the activated T cells. As with DSP and envoplakin, PPL has spectrin and plakin domains and has globular motifs. PPL interacts with Dsg1 and desmoglein 3, envoplakin, DSP, ezrin, periaxin, neuroblast differentiation-associated protein, and kazrin. These are components of the CCE of keratinocytes. PPL has an N-arginine dibasic convertase domain; in Supplementary

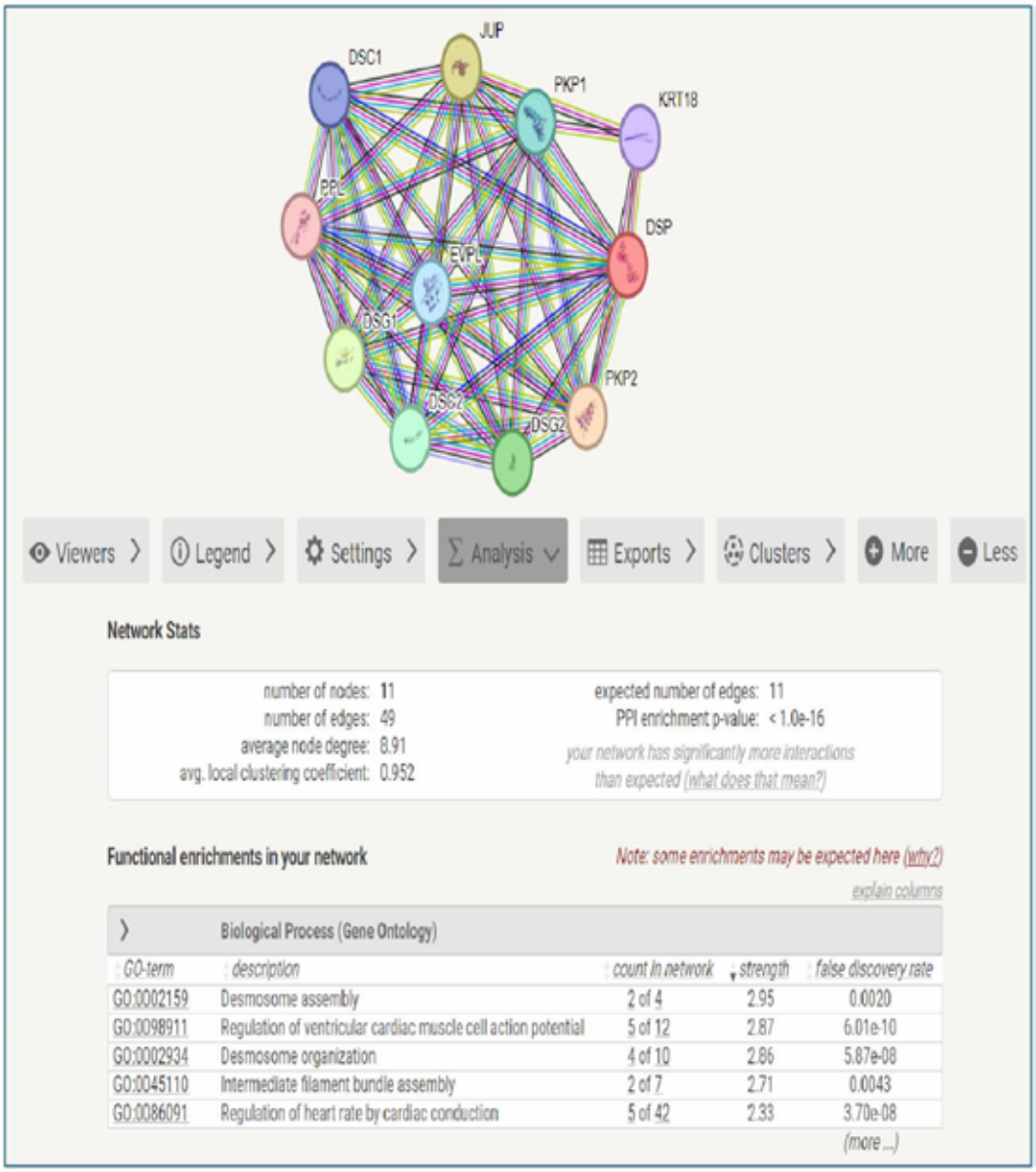

Figure 3. Interaction nodes for DSP.
Credits: https://string-db.org/cgi/network?taskId=buJXa8B5RtVY&sessionId=bMuCFyhY1ngL

File 1, we present the interacting node proteins for PPL. The PPL network contains 132 interaction nodes and 1440 physical entity nodes.

Bullous Pemphigoid Antigen 1 (BP230)

UniProt name Q03001-7. DYST_HUMAN, Dystonin. BP230 has 7570 aa. BP230 functions as cytoskeletal linker protein and as an integrator of IF, actin, and microtubule cytoskeleton networks. BP230 is required for anchoring IF to the actin in neural and muscle cells and keratin-containing IF to hemidesmosomes in epithelial cells. BP230 self-aggregates to form filaments as a two-dimensional mesh. BP230 regulates the organization and stability of the microtubule network of sensory neurons to allow axonal transport; it also assists in wound healing. BP230 mediates docking of the dynein/dynactin motor complex to vesicle cargos for retrograde axonal transport through its interaction with TMEM108 and DCTN1. Similar to DSP, envoplakin, and PPL, BP230 has spectrin as well as plakin domains, and a calponin homology domain. BP230 also has an EF-hand, calcium binding motif. Like Dsg1, DSP, and envoplakin, BP230 also has CS-3 and CS-7 cleavage sites. B230 displays loops and helices in its secondary structure. BP 230 has nine IS. In Supplementary File 2, we present the interacting nodes of BP230. The BP230 IS 1 interacts with desmin. IS 1 interacts with spectrin repeat containing nuclear envelope family member 3. IS 1 and IS 6 homodimerize via their N-terminus. IS 1 interacts via its N-terminus with actinin alpha 2. IS 1 works together via its N-terminus with the plectin N-terminus. IS 3 interacts via its N-terminus with the alpha chain of Type XVII collagen

(COL17A1) via its cytoplasmic region. IS 3 interacts via its N-terminus with beta 4 Integrin. IS 3 interacts via its N-terminus with ERBIN via its C-terminus. IS 3 associates via its C-terminus with cytokeratins 5 and 14 (via the rod region). IS 3 interacts with microtubule-associated protein RP/EB family member 1 and with transmembrane and immunoglobulin domain containing 2 protein (CD28H). IS 3 plays a structural role in the assembly of hemidesmosomes of epithelial cells and anchors keratin-containing IF to the inner plaque of hemidesmosomes. IS 3 is required for the regulation of keratinocyte polarity and motility and mediates integrin ITGB4 regulation of RAC1 activity. IS 6 is required for bundling actin filaments around the nucleus. IS 7 regulates the organization and stability of the microtubule network of sensory neurons to allow axonal transport. IS 9 interacts with transmembrane protein 108, associated with Alzheimer disease. BP230 also has protein homodimerization activity and has an integrin-mediated signaling pathway for ending regulation. In Supplementary File 2, we show BP230 having more than 2,000 interactions. BP230 undergoes downstream cellular processing and is a calcium and metal binding protein. Dystonin is likewise part of the lipid bilayer surrounding the endoplasmic reticulum membranes. BP230 is part of the cell-substrate junctions that anchor the cell to the extracellular matrix and form a point of termination for actin filaments (focal adhesion). BP230 is part of the Z disk of the heart. BP230 is part of the desmosomes and the H zone (H disk, H band). BP230 has been located in the nuclear envelope and in the nucleoplasm.

Plakophilin-4 (p0071, PKP4)

UniProt name: Q99569. PKP4, p0071. It has 1,192 aa, and a mass of 131,868 Da. The known functions of PKP4 is to play a role as a regulator of Rho activity during cytokinesis as well as the attachment in junctional plaques. PKP4 has PTM modifications including methylation and phosphorylation. PKP4 has Armadillo/beta-catenin-like repeats and globular motifs. The armadillo repeat is in approximately 40 amino acids, tandemly repeated sequence motif involved in signal transduction. PKP4 interacts with ATP synthase, mitochondrial F1 complex assembly factor 2, as a peripheral membrane component of the cis-Golgi stack (a membrane skeleton that preserves the structure of the Golgi apparatus), and a vesicle tether that facilitates vesicle fusion to the Golgi membrane. PKP4 additionally regulates meiotic spindle pole assembly and centrosome organization. PKP4 interacts with the E3 ubiquitin-protein ligase TRIM23-HUMAN, a GTP-binding protein of ARD-1 type. PKP4 also binds protein scribble homolog, leucine zipper putative tumor suppressor 2, and discs-large homolog 1. In Supplementary File 2, we show that the PKP4 network contains 104 interaction nodes and 2568 physical entity nodes. We present the respective interactions, complexes, compounds, and gene(s).

Myocardial Zonula Adherens Protein (MYZAP)

UniProt name: P0CAP1. GRINL1A upstream protein (Gup), Myocardium-enriched zonula occludens-1–associated protein (Myozap), and MYZAP. MYZAP has a of 466 aa and a mass of 54,206 Da. The encoded protein localizes to the intercalated discs in cardiomyocytes and functions as an activator of Rho-dependent serum-response factor signaling. MYZAP alternative splicing results in multiple transcript variants. Readthrough transcription also exists between this gene and the neighboring downstream gene POLR2M II polypeptide M. The MYZAP network contains 27 interaction nodes and 149 physical entity nodes. MYZAP has a LIG_TRAF3_MATH_PxP_3 Ring finger E3 ligase TRAF2; it specifically interacts with TNF receptor superfamily members and connects the receptors to downstream signaling proteins. Additionally, MYZAP contains a central ezrin-radixin-moesin protein domain. MYZAP function also includes a role in cellular signaling via Rho-related GTP-binding proteins and subsequent activation of the transcription factor SRF. MYZAP links with the tight junction protein ZO-1. In cortical neurons, MYZAP may play a role in glutaminergic signal transduction through interaction with the N-methyl-D-aspartate receptor (NMDA, or NMDAR) subunit GRIN1. NMDA is a glutamate receptor and an ion channel in neurons. Depending on its subunit composition, its ligands are glutamate and glycine or D-serine. The binding of the ligands is typically not sufficient to open the channel as it may be blocked by Mg^{2+}ions, which are removed only when the neuron is sufficiently depolarized. The NMDA receptor is ionotropic, meaning it is a protein which allows the passage of ions through the cell membrane. MYZAP interacts with the Rho-related GTP-binding protein Rho6, but it lacks intrinsic GTPase activity. MYZAP interacts with DSP, PKP2, plectin, catenin beta-1, TJP1, ZO-1, and DYNLL1. MYZAP interacts with the mediator of RNA polymerase II transcription subunit 26, involved in the regulated transcription of nearly all RNA polymerase II-dependent genes. MYZAP interacts with myosin phosphatase Rho-interacting protein, which inhibits the activation of transcription factor SRF. MYZAP interacts with RNA polymerase II, holoenzymes, nuclear envelopes, anchoring junctions, maintenance of ER location, and is a part of the Z disks. The adjacent MYZAP and DNA-directed RNA polymerase II subunit GRINL1A genes are a part of a complex transcription unit. The respective transcripts derive from different promoters and are alternatively spliced. In Supplementary File 2, we present the interacting node features of MYZAP.

MYZAP has 11 confirmed IS: P0CAP1-1, (Gcom8, Gup1) interacting with MYBPC3, DYNLL1, RPGRIP1L;

P0CAP1-2. 2. (Gcom2). 445 aa, 51,824 Da. P0CAP1-3. (Gcom13), 435 aa, 50,381 Da; P0CAP1-3 (Gcom13), 435 aa, 50,381 Da; P0CAP1-4, (Gcom9, Gup2), 438 aa, 50,913 Da; P0CAP1-5 (Gcom10), 390aa, 45,519 Da; P0CAP1-6 (Gcom3) 414aa, 48,149 Da; P0CAP1-7 (Gcom4), 407 aa, 47,397 Da; P0CAP1-8 (Gcom5), 379 aa, 44,104 Da; P0CAP1-9 (Gcom6), 415 aa, 48,231 Da; P0CAP1-10 (Gcom11), 397 aa, 46,224 Da; P0CAP1-11 (Gcom1, GRINL1A complex locus protein 1). 550 aa, 64,046 Da. There are also two other potential isoforms. MYZAP has both coiled and globular motifs.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVCF)

UniProt name O00192, splicing regulator ARVCF. 962 aa amino acids, 104,642 Da. ARVCF is a delta catenin family member. The ARVCF function is to participate in the regulation of alternative splicing of pre-mRNAs. Interaction of the ARVCF subunit and ribonucleoprotein complexes containing mRNAs and RNA-binding proteins include DDX5, HNRNPH2, and SRSF1. ARVCF has two known PTMs, including phosphorylation and methylation. ARVCF has two potential isoforms and has coiled-coiled regions, arm repeats, and globular regions. In Supplementary File 2, we show that the ARVCF network contains 38 interaction nodes and 340 physical entity nodes.

Discussion

In this study, we focused on protein-protein interactions and utilized websites including UniProt, RCSB PDB, ConsensusPathDB, String, PhosphoSitePlus, and others [3-17]. Current internet platforms for studying protein-protein interactions have limitations in addressing the complexity of these interactions (e.g., folding, dimerism), interacting substrates, enzymatic functions, and/or protein biochemical changes occurring in vivo. Our study suggests that these platforms require global cooperation, and they should ideally be accessible free to the public. Protein interactions require correlation with Co-IP, yeast two-hybrid methods, and mass spectrometry, and the results should be shared [2].

We attempted to attain comprehensive knowledge regarding how the known El Bagre-EPF antigens interact as physical entities. Multiple protein antigens are embedded in the bi-layered cell membrane and/or intracellularly. At present, secondary lipid and protein interactions are not taken into consideration in lipid-protein interactomes. Indeed, this area of knowledge remains uncharted. We identified accessible databases relating to protein interactions with DNA and RNA; however, some platforms and software need improvement [18].

In the current study, we also confirmed that specific El Bagre-EPF antigens are part of multiple cell junctions and cell membranes. These antigens have plasma membrane, intracytoplasmic, nuclear and nucleolar locations as well as enzymatic sites and cell signaling motifs. Individual El Bagre-EPF antigens are present in cell junctions and IF networks [19]. These are not coincidental locations. Several autoantigens have spectrin as well as plakin domains and catalase sites; some of them possess similar post-translation modifications, and a majority have calcium binding and immunoglobulin domains.

The El Bagre EPF disease is autoimmune in nature. The development of autoimmunity requires a genetic anomaly, as in lupus [20]. It has been considered that the development of autoimmunity may be due to molecular mimicry (similarity between an external environmental triggering factor and the patient's native proteins). In addition to genetic factors, environmental triggering factors (including infectious ones) remain to be determined in El Bagre-EPF [21].

Our study revealed a complex network of physical interactions among the El Bagre-EPF antigens. Previously, it had been demonstrated that desmosomal transmembrane core and plaque molecules as well as that ARVCF and plakophillin 4 were part of the vertebrate p120-catenin subfamily made up of four proteins [22-27]. Functionally, Arm repeats allow for the attachment of catenins to classical cadherins and are one of the sites of connections with small Rho GTPases. In addition, Arm repeats are part of several proteins that act as "on-off" switches in signal transduction; these proteins include the Rho protein family, GTPases, small GTPases, and others [22-27].

Conclusions

Our study confirms the physical proximity of El Bagre-EPF antigens and their roles in modulating cell junctions, plaque formation, and the cytoskeleton. They also enable additional functions, such as stabilizing cadherin-catenin complexes at AJs, and contain motifs that participate in cell signaling pathways and enzymatic sites. We also found that current platforms for studying interactomes and post-translation modifications fall short in accurately reflecting in vivo conditions. A focus on lipid-protein secondary interactions may help improve interactome utility.

Abbreviations: Endemic pemphigus foliaceus (EPF), endemic pemphigus foliaceus in El Bagre (El Bagre-EPF), tridimensional (3D), desmoglein 1 (Dsg1), periplakin (PPL), plakophilin 4 (p0071, PKP4), bullous pemphigoid antigen 1 (BP230), adherens junctions (AJ), intermediate filaments (IF), Armadillo Repeat gene deleted in Velo-Cardio-Facial syndrome (ARVCF), desmoplakins 1-2, (DP I-II),

myocardium-enriched zonula occludens-1-associated protein (MYZAP), Daltons (Da), desmocollin-1; (DSC1), corneodesmosin (CDSN), junction plakoglobin (JUP), plakophilin-2 (PKP2), plakophilin-3 (PKP3), desmocollin-3, (DSC3), post-translational modifications (PTM), caspase (CS), isoform (IS), aminoamides (AA), cornified cell envelope (CCE).

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