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Nucleic acid-binding KH domain proteins influence a spectrum of biological pathways including as part of membrane-localized complexes

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ABSTRACT

K-Homology domain (KH domain) proteins bind single-stranded nucleic acids, influence protein–protein interactions of proteins that harbor them, and are found in all kingdoms of life. In concert with other functional protein domains KH domains contribute to a variety of critical biological activities, often within higher order machineries including membrane-localized protein complexes. Eukaryotic KH domain proteins are linked to developmental processes, morphogenesis, and growth regulation, and their aberrant expression is often associated with cancer. Prokaryotic KH domain proteins are involved in integral cellular activities including cell division and protein translocation. Eukaryotic and prokaryotic KH domains share structural features, but are differentiated based on their structural organizations. In this review, we explore the structure/function relationships of known examples of KH domain proteins, and highlight cases in which they function within or at membrane surfaces. We also summarize examples of KH domain proteins that influence bacterial virulence and pathogenesis. We conclude the article by discussing prospective research avenues that could be pursued to better investigate this largely understudied protein category.

The K homology domain

The K Homology (KH) domain (pfam: PF07650) is a protein domain that was first discovered in human heterogeneous nuclear ribonucleoprotein K (hnRNPK). This protein domain family is comprised of an evolutionarily conserved sequence of roughly 70 amino acids found in a wide range of nucleic acid (NA)-binding proteins. KH domains have been reported to bind RNA as well as ssDNA, and are employed for small, ribosomal, transfer, and messenger RNA recognition (Hollingworth et al., 2012; Haskell and Zinovyeva, 2021; Tu et al., 2009a; Legault et al., 1998). They are found in multiple copies in several known proteins, and can operate cooperatively or independently (García-Mayoral et al., 2007). For example, two KH domains are found in human Fragile X Mental Retardation Protein (FMRP) (Myrick et al., 2015), three in eukaryotic hnRNPK (Ostareck-Lederer and Ostareck, 2004), and fourteen in vigilin (Dodson and Shapiro, 1997). Several examples of proteins with only a single KH motif include yeast Mer1p (Spingola et al., 2004), human RNA metabolism protein Sam68 (Lukong and Richard, 2003), and *Clostridiodes difficile* KhpA and its *Streptococcus mutans* ortholog Smu_866 (Zhu et al., 2023). Nuclear magnetic resonance (NMR) solution structures of the earliest characterized KH domains, those within FMRP and the C-terminal KH domain of hnRNPK, revealed a beta-alpha-alpha–beta-beta-alpha structure (Musco et al., 1997). To date, numerous different individual KH domains have been shown to act as NA recognition motifs within their parent proteins in both eukaryotes and prokaryotes thereby helping to mediate physiologic tasks that require NA-protein interactions.

KH domain containing proteins are found in several locations within prokaryotic and eukaryotic cells, often as integral membrane proteins or associated with membrane protein complexes. This theme will represent a major focus of this review. KH domains represent tunable motifs that balance functional diversity with NA specificity, and as a result are used in many different biological processes. KH domains are found in proteins central to both transcriptional and translational control, as well as other cellular activities such as genetic competence, RNA metabolism, membrane transport, and cell division, etc. (Vasquez et al., 2021; Hahn et al., 1993; Hare et al., 2007; Cho, 2017). Several human disorders, including Fragile X Mental Retardation Syndrome, Chopra-Amiel-Gordon Syndrome, and paraneoplastic sickness, are all linked to the loss of function of a given KH domain (Musco et al., 1997; Chopra et al., 2021; Lewis et al., 2000). The recognition of participation of KH domain proteins in additional critical cellular pathways is expected to increase as more

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studies are conducted.

Types and nucleotide specificity of KH domains

As illustrated in Fig. 1, KH domains are classified into two categories, Type I and Type II, based on their structural characteristics (Grishin, 2001). Type I domains are found primarily in eukaryotic proteins, whereas Type II domains are mostly found in prokaryotic proteins. While both types share a minimum consensus pattern, the organization of their structural folds differ. The Type I KH fold is distinguished from the Type II fold by an all-antiparallel strand arrangement. In addition, multiple Type I KH domains are frequently found within a given single protein, whereas Type II domains are usually located as a single unit within the parent protein (Valverde et al., 2008). Type I and Type II KH domains differ in terms of their variable loops' lengths and sequences. Although occasionally modified in atypical KH domains, the typical NA-interacting GXXG loop is located between flanking α1 and α2 segments. It is noteworthy that the minimal KH organizational motif is generally found at the N-terminus of Type I KH domains, while it is usually located at the C-terminus of Type II KH domains (Olejniczak et al., 2022). The functional significance of such distinct organizational differences on NA-binding or other activities is not yet understood.

The NA-binding ability of KH domains is essential in order to enable each parent protein's specific biological activities. Individual KH domains tend to be unique in their identification of particular NA sequences. Early solution NMR structure analysis of the hnRNPK KH3 domain revealed a variable binding cleft that accommodates four bases (Braddock et al., 2002a). This is unlike other RNA recognition motifs that can recognize a wide range of RNA lengths (Afroz et al., 2015). The NA-binding affinity of KH domains is influenced by van der Waals forces, hydrophobic interactions, and to a lesser extent electrostatic interactions. Multiple tandem KH domains, each containing their own GXXG motifs, in conjunction with other nearby structural motifs, can be used to influence the composite recognition surface when greater specificity for particular combinations of four bp sequences is needed. For example, solution NMR structure analysis of the KH3 and 4 domains of mammalian KSRP (KH-type Splicing Regulatory Protein) demonstrated that these two domains operate as distinct binding modules to engage with separate areas of their AU-rich mRNA targets (García-Mayoral et al., 2007).

The bulk of our current understanding of KH domain interactions with ssNA comes from research on proteins from the eukaryotic world. As illustrated in Fig. 2A, the current structural model depicts target RNA or ssDNA bound in an extended, single-stranded conformation across one face of the KH domain, between the alpha 1 and 2 helices and GXXG segments shown to the left, and the beta sheet segments and variable loop shown to the right. These secondary structural elements operate together to generate the NA- binding cleft. The variable loop of a Type II KH domain is positioned at the bottom of the NA-binding cleft, which distinguishes it from a Type I KH domain (see Fig. 1). The hydrophobic core of a KH domain NA-binding groove (human alpha poly(C)-binding protein KH1) is illustrated in Fig. 2B. NA-binding can be stabilized by additional specific interactions, for example the adenine to protein backbone hydrophobic interaction observed by X-ray crystallography of *Mycobacterium tuberculosis* NusA bound to RNA (Beuth et al., 2005). Interestingly NA base-to-protein aromatic side-chain stacking interactions, which are commonly observed in other types of single-stranded NA-binding motifs (Stefl et al., 2005; Nagai, 1996), are conspicuously lacking from KH domain-mediated NA recognition. Whether this manifests as reduced NA-binding affinity of KH domains compared to other NA-binding motifs remains to be tested.

The underlying basis for the varying nucleotide binding specificities observed among typical KH domains is also not yet well understood. KH domain proteins demonstrate a range of nucleotide sequence preferences. As stated above, a single KH domain typically binds four nucleotides. Several studies of eukaryotic KH domain-containing proteins suggest that the recognized nucleotides are often C and T at positions 1 and 4, and A and C at positions 2 and 3 (Lewis et al., 2000; Liu et al., 2001; Braddock et al., 2002b; Du et al., 2005). However, atypical KH domain binding to completely different NA sequences has also been found. For example, the third KH domain of the human K homology Splicing Regulator Protein (KSRP) (PDB:4B8T) binds a G-rich sequence within the *let-7* microRNA required for developmental timing from nematodes to humans (Lee et al., 2016a), and forms a KH-AGGGU

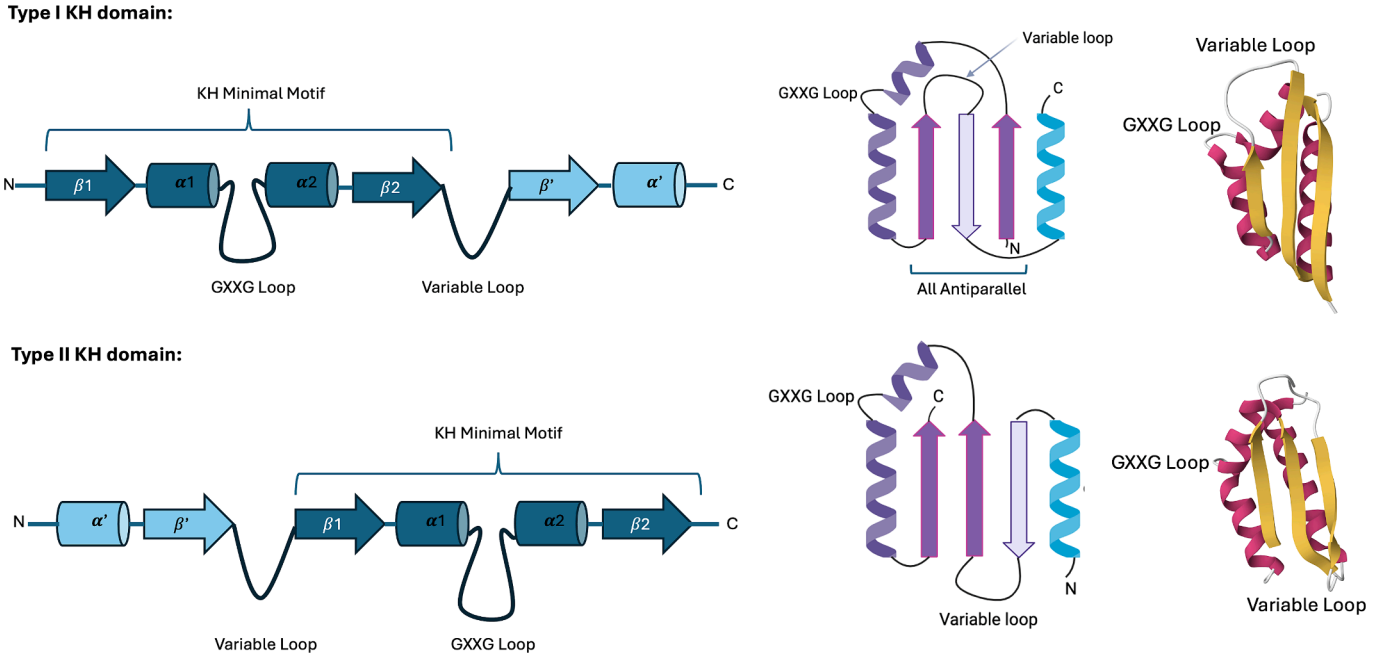

Fig. 1. Schematic representation of Type I compared to Type II KH domains. Type I domains are characterized by a completely anti-parallel arrangement of their β-strand segments. In addition, the variable loops of Type I and Type II KH domains fall on opposite sides of the folded structure and are oriented either in proximity or away from the GXXG NA-binding motif. Lastly, the KH domains generally fall at the N-terminus of Type I proteins and at the C-terminus of Type II proteins.

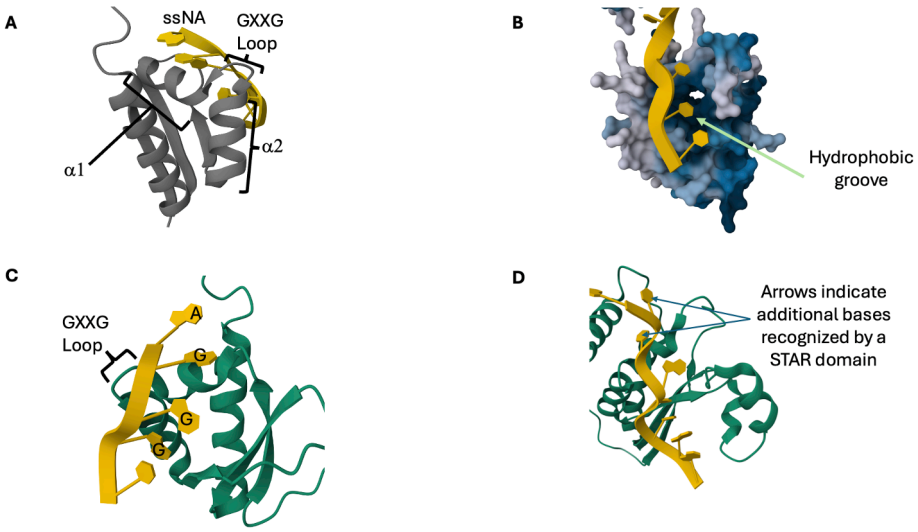

Fig. 2. Models of KH domain bound to a target ssNA. A. The folded structure of a model KH domain is illustrated in grey. The NA-binding GXXG loop that falls between the α1 and α2 helices is marked, and the target ssNA is illustrated in yellow. B. The hydrophobic NA-binding groove is depicted in darker purple based on X-Ray diffraction structure analysis of a KH domain of human poly(C)-binding protein bound to its target RNA (PDB: 1ZTG). C. Illustration of atypical NA sequence recognition by the third KH domain of KSRP (PDB: 4B8T). Instead of the typical T/U and C base interaction, this KH domain interacts with G-rich RNA. D. An X-ray crystallographic structure of a STAR domain (PDB: 4JVH) bound to its cognate RNA recognition element whereby the canonical KH domain's GXXG groove is extended to allow recognition of two additional nucleotides. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

complex (Trabucchi et al., 2009; Nicastro et al., 2012; García-Mayoral et al., 2008) (Fig. 2C). Also, the observation that KH domains recognize and interact with only four bases is not universal. For example in the STAR (Signal Transduction and Activation of RNA) fold, which mediates RNA recognition within a family of proteins important for mRNA splicing, the interacting sequence of the RNA partner is six bases long (Lin et al., 1997). An X-ray crystallographic structure of a STAR domain bound to its cognate RNA recognition element demonstrated that in this composite domain the canonical KH element GXXG groove is extended to allow recognition of two additional nucleotides (Teplova et al., 2013; Beuck et al., 2012) (Fig. 2D). The Type 2 KH domain within the bacterial ribosome biogenesis factor Era, a GTPase protein, takes this expansion even further by recognizing a sequence of nine NA residues, five of which are positioned outside of the NA-binding groove. That is, this particular KH domain interacts specifically with NA residues apart from those that fall within a typical NA-binding groove (Tu et al., 2009a). In summary, multiple factors are now known to contribute to the specificity of a given KH domain-NA interaction. This level of complexity thus far precludes easy prediction of NA target sequences of particular KH domains, although continued analysis of solved structures of KH domain-NA complexes in conjunction with machine learning tools may help to make this goal a reality.

Affinity of KH domains for NA targets

KH domains have been measured to have low micromolar NA affinity suggesting that their interactions are transient. Using isothermal titration calorimetry Liu et al. determined the dissociation constant (Kd) of a complex including the human splicing factor 1 protein's KH domain interaction with the intron Branch Point Sequence (BPS) UACUAAC to be ~ 3 uM (Liu et al., 2001). On the same order of magnitude, hnRNPK's KH3 domain interaction with a 10mer ssDNA has a reported Kd value of ~ 1 uM (Braddock et al., 2002a). These results are consistent with Kds, measured by electrophoretic migration shift assay, of ~ 1.5 uM and ~ 2.5 uM for interactions of the DEAD-box helicase protein DDX43 with ssDNA and ssRNA, respectively (Yadav et al., 2021). One way that KH domain proteins can boost their affinities for ssNA is through domain clustering, which also serves to enable more specific interactions with target NAs (Lunde et al., 2007). For example, the four tandem KH domains of *Drosophila* P element Somatic Inhibitor (PSI) cooperate to bind specifically to the protein's pre-mRNA ligand (Chmiel et al., 2006). Another example of multiple KH domains working in concert to promote ssRNA binding is the human K homology Splicing Regulator Protein (KSRP). In a series of NMR and circular dichroism experiments, researchers demonstrated that this protein's third and fourth KH domains interact with the RNA ligand more tightly than does a single domain (García-Mayoral et al., 2007). Again, the KH-domain-containing bacterial protein, NusA from *M. tuberculosis,* combines two KH domains to form an uninterrupted recognition surface thereby increasing the affinity for ssRNA to nanomolar levels (Beuth et al., 2005). In examples in which the structures of both the KH-NA complex and the free KH domain have been solved, the interaction with NA caused little to no observable structural change in the protein. X-ray crystallographic analyses of the KH domains of the Nova-2 protein (responsible for RNA metabolism in neurons) bound to its cognate RNA, and the human poly(C)-binding protein-2 bound to a C-rich strand of human telomeric DNA, showed no detectable differences in 3D structures compared to their respective unbound forms (Lewis et al., 2000; Du et al., 2005). Whether this is a common feature among all KH domains is not yet known and would require further structural analyses of additional KH domains in NA bound/unbound forms to determine. Despite the fact that isolated KH domains have been reported to crystallize as monomers, dimers, and even tetramers, there is not yet direct experimental evidence to demonstrate that KH domains produce noncovalent higher-order oligomers under biological conditions (Valverde et al., 2008).

Membrane associations of KH domain proteins

KH domain proteins are localized to different areas within a cell in accordance with the particular functions that they perform. In this review we highlight some of the better characterized KH domain proteins and focus on examples that are membrane-localized or associated because, as summarized in Table 1, it is coming to light that a substantial number represent either integral membrane proteins or function as part of membrane-associated complexes. As illustrated in Fig. 3, eukaryotic KH domain proteins have been reported to partition with nuclear and

Table 1
Summary of KH domain protein components of membrane-localized complexes in eukaryotic and prokaryotic organisms.

Protein	Organism/tissue	Membrane localization/relevance	# of KH domains	Mutation phenotype	Known NA target
Eukaryotic examples:					
FMR1	*Homo sapiens*, highly expressed in nervous system	Membrane- associated	3	Mental Retardation	ACUK (K = G/U) of UBE3*A* mRNA
KHNYN	All vertebrates	Endomembrane associated via ZAP	1	Reduced antiviral resistance	Clustered CpG dinucleotide of viral genome
AKAP1	All eukaryotes	Associated with mitochondrial outer membrane	1	Pleiotropic stemming from mitochondrial dysfunction	UCUUA of 3′ UTR of *star* mRNA
ANKHD1	*H. sapiens,* highly expressed in cervix, spleen, and brain	Associated with endosomal membrane	1	Aberrant development	LINC00346 long non-coding RNA
hnRNP	*H. sapiens*	Membrane-associated via CAVIN1	3	Au–Kline syndrome	UAGGG at 5′ SS in intron 9 of PKM
Khd4	Fungi	Regulates membrane trafficking	5	Aberrant cell morphology and vacuole biogenesis	3′ UTR AUACCC of um10914
PNPase	Animal/Plant	Associated with mitochondrial inner membrane	1	Hearing loss	Long 3′ tail of 5S rRNA, MRP RNA, and RNaseP RNA
HDLBP	*H. sapiens*	Cytoplasmic face of the endoplasmic reticulum membrane	15	Promotes sarcomagenesis	CU-rich region of ApoB, ApoC-III mRNA
Scp160	Yeast	Associated with nuclear membrane/ endoplasmic reticulum	14	Aberrant cell morphology	5′ UTR UGAAAAAUUUU of mRNAs
Prokaryotic examples:					
KhpA	Mostly Gram-positive and some Gram-negative bacteria	Membrane association *via* KhpB interaction	1	Abnormal cell division, cell morphology	CA rich sequence of 5′UTR of *ftsA*
KhpB	Mostly Gram-positive and some Gram-negative bacteria	Membrane association *via* SpoIIIJ/ YidC interaction	1	Abnormal cell division, cell morphology	5′ UTR of *tcdA* mRNA
PNPase	Gram-positive and Gram-negative bacteria	Inner/cytoplasmic membrane component of RNA degradasome	1	Increased susceptibility to cold shock	Poly A tails of numerous mRNAs
RNaseY	Firmicutes and ε–proteobacteria	Integral membrane protein	1	Smaller colony, slower growth	5′ UTR of rpsO mRNA
HofQ	*E. coli, H. influenzae, A. actinomycetemcomitans*	Integrated into outer membrane	1	Slower growth, reduced competence	5′AAGTGCGGT sequence of extracellular DNA
Era	Gram-positive and Gram-negative bacteria	Inner surface of cytoplasmic membrane	1	Essential/ Growth defect and abnormal morphology	3′ GAUCACCUCC sequence of 16S rRNA
CvfA	Gram-positive bacteria	Cytoplasmic membrane integrated	1	Reduced virulence	3′ end of *sae* operon transcripts

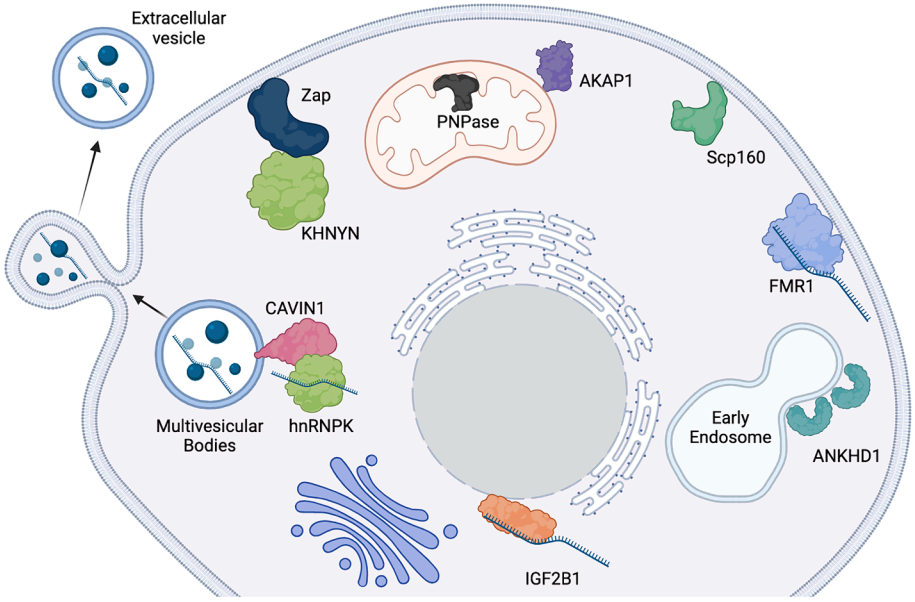

Fig. 3. Examples of membrane-localized eukaryotic KH domain proteins. A simplified eukaryotic cell is shown to illustrate the variety of cellular and organellar membranes that harbor KH domain proteins directly, or as components of membrane protein complexes, as discussed individually in this review and summarized in Table 1.

cytoplasmic membranes, endoplasmic reticulum, multivesicular bodies, and endosomes, as well as with extracellular vesicles (exosomes). In prokaryotic cells, examples of KH domain proteins have been found as components of membrane protein complexes of both outer and inner membranes of Gram-negative organisms, as well as the cytoplasmic membrane of numerous Gram-positive species (Fig. 4). Prokaryotic KH

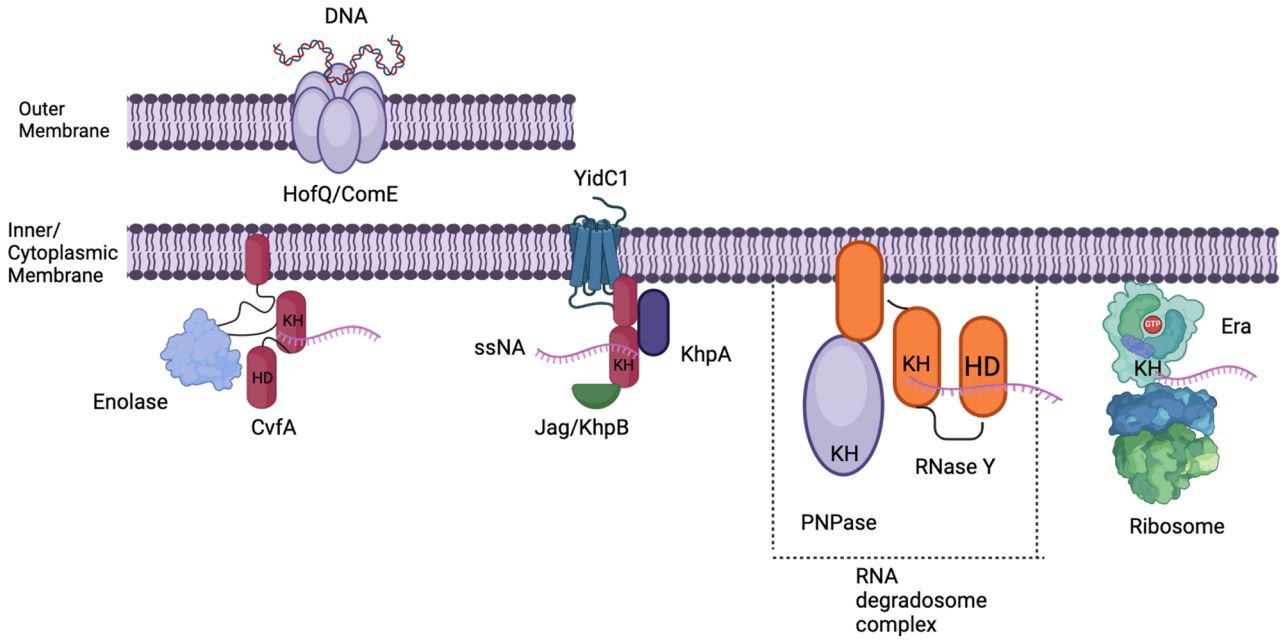

Fig. 4. Examples of membrane-localized prokaryotic KH domain proteins. A number of examples of KH domain proteins that are embedded in or associated with the outer membrane of Gram-negative bacteria, or the inner membrane of Gram-negative bacteria or cytoplasmic membrane of Gram-positive bacteria, are known. These have each been discussed individually in this review and are summarized in Table 1. The KH domains of HofQ (ComE) are exposed on the outside of the cell enabling interaction with extracellular DNA. The KH domain-containing proteins RNase Y and PNPase are components of the RNA degradosome complex. Bacterial CvfA and Era are each known to contribute to virulence in animal models. Jag (KhpB) has been identified as an interaction partner of the integral membrane protein YidC1 involved in membrane protein transport. KhpA also interacts with Jag.

domain proteins have been linked to diverse functional machineries including those contributing to genetic competence, cell division and morphology, membrane protein insertion, ribosome biogenesis, and processing and degradation of mRNA. Our current listing herein of membrane-localized KH domain proteins is not exhaustive and more examples will likely be discovered with continued study of this protein family. An increased focus needs to be placed on delineating structural features of membrane-associated versus cytoplasmic KH domain proteins and consequent influences on binding of KH domain NA targets.

Membrane-associated eukaryotic KH domain proteins

One of the best studied examples of a membrane-associated KH domain protein in eukaryotes is the Fragile X Mental Retardation gene product (FMR1) (PDB: 2FMR) in which early structure analysis was accomplished using solution NMR (Musco et al., 1997). In humans, FMR1 deficiency results in significant learning difficulties or intellectual disabilities, as well as physical abnormalities characteristic of fragile X syndrome (Majumder et al., 2020). A person with residue Ile304 mutated to Asn within the KH2 domain of FMR1 displays a particularly severe form of the disease (Valverde et al., 2007; Musco et al., 1997). However, how this particular mutation influences FMR1 RNA binding is not well understood. FXR1 and FXR2 are two additional members of this KH domain protein family (Majumder et al., 2020). Fluorescence anisotropy RNA binding assays have shown that FMR1 KH domains bind WGGA (W = A/U) and GACR (R = A/G) sequences. FMR1 is a component of a large mRNP (messenger ribonucleoprotein) complex where it is suspected to perform nucleocytoplasmic shuttling of target mRNAs (Athar and Joseph, 2020). This protein was previously shown to partition with a heavy membrane fraction that included the plasma membrane, mitochondria, and nuclear membrane (Taha et al., 2014).

The Ankyrin (ANK) repeat family of proteins, including AKAP1, ANKHD1, and ANKRD17, also contains KH domains that bind single-stranded RNA or DNA. The cAMP-dependent protein kinase PKA mediates hormonal effects on cellular respiration (Ginsberg et al., 2003), and localizes to membranes, the cytoskeleton, and cellular organelles *via* direct contact with A-kinase anchor proteins (AKAPs) (Grozdanov and Stocco, 2012). AKAPs anchor PKAs to the mitochondrial outer membrane surface to enable enhanced cAMP signaling activity. AKAP1 contains a PKA R2 binding domain, as well as an RNA-binding KH domain (Gabrovsek et al., 2020), which has a reported specificity of UCUUA based on SELEX (systematic evolution of ligands by exponential enrichment) technology (Grozdanov and Stocco, 2012). The protein's KH domain has also been demonstrated to bind to distinct nuclear-encoded mRNAs, including within the 3′ UTRs of transcripts that encode manganese superoxide dismutase (MnSOD) and the membrane-localized f subunit of human ATP synthase. Such mRNA binding results in increased levels of mitochondrial SMOD (Ginsberg et al., 2003), as well as increased synthesis of ATP (Carlucci et al., 2008).

AKAP1 is also documented to modulate mitochondrial fission (Edwards et al., 2020). The KH domain protein ANKHD1 interacts with other proteins involved in various critical signaling pathways, including receptor tyrosine kinase, JAK/STAT, mechanosensitive Hippo (YAP/TAZ), and p21 (Mullenger et al., 2023). According to studies in mice, ANKHD1 plays a role in liver development (Lee et al., 2016b). Again, impairment of its KH domain function is associated with aberrant development albeit with little understanding of the underlying mechanism. ANKHD1 has been reported to contribute to production of endocytic vesicles, and was observed to interact with early endosome membranes and to dimerize *via* ANK domains to deform the membranes into tubules and vesicles (Kitamata et al., 2019). The specific role of the KH domain in this process is not yet known. Autosomal dominant Chopra-Amiel-Gordon syndrome, which is characterized by impaired intellectual development, speech delay, and facial dysmorphism in humans is caused by *de novo* mutations within ANKRD17 (Chopra et al., 2021). The number of solved structures of ANK proteins is relatively low, likely as a consequence of their high molecular weights. To date, no structural analyses of KH domains of AKAP1, ANKHD1 or ANKRd17 interacting with their cognate target NAs have been performed.

Eukaryotic hnRNP (heterogeneous nuclear ribonucleoprotein)

proteins form complex with heterogeneous nuclear RNA (hnRNA) (Lu and Gao, 2016). These proteins influence pre-mRNA processing as well as other aspects of mRNA metabolism and transport. hnRNPK protein have distinct NA-binding properties that are mediated by three repeats of KH domains (Lu and Gao, 2016). The structure of the KH domain of hnRNPK in association with ssDNA has been solved by X-ray crystallography (hnRNPK PDB: 7CRE). It was demonstrated to associate with RNA *via* multiple weak interactions (Yao et al., 2021). Mutations in both copies of *hnRNPK* in diploid cells are embryonic lethal in mice (Gallardo et al., 2015), whereas mutation of a single copy causes Au–Kline syndrome characterized by hypotonia, learning disability, and delayed development (Au et al., 1993). Deficiencies in hnRNPK result in reduced levels of the cyclin-dependent kinase inhibitor 1 (p1), which is involved in pausing cell development for DNA repair by way of a pathway that also includes the p53 tumor suppressor (Gallardo et al., 2015). Not surprisingly considering hnRNPK's role in cell cycle progression, its overexpression is thought to contribute to cancer (Au et al., 1993; Robinson et al., 2021; Bell et al., 2013). In human cells, hnRNPK is believed to be responsible for sorting miRNAs for transport to the exosome via its interaction with a key membrane lipid raft protein, cytoplasmic protein cavin-1 (CAVIN1) (Robinson et al., 2021). Again, this highlights the increasing recognition that KH domain proteins often function within or in close proximity to cellular membranes (see Table 1 and Fig. 3).

The vigilin family member protein HDLBP (high-density lipoprotein binding protein) harbors 15 KH domains and is generally found on the cytoplasmic face of the endoplasmic reticulum membrane (Vollbrandt et al., 2004). Numerous processes, including translation, chromosomal segregation, cholesterol transport, and carcinogenesis, are impacted by HDLBP. The absence of HDLBP was reported to result in the decrease (n = 700) and increase (n = 1039) of mRNAs in HEK293 immortalized human embryonic kidney cells, emphasizing the broad impact of HDLBP on many hundreds of transcripts (Zinnall et al., 2022). The majority of the target mRNAs of HDLBP encode proteins that are either localized within the membrane or released as part of the endomembrane system. It is known that the presence of a CU-rich region is necessary for HDLBP binding to mRNAs encoding ApoB, ApoC-III, and the glycoprotein fibronectin (Mobin et al., 2016). No structural information yet exists regarding these interactions. Levels of ApoB and ApoC-III, two proatherogenic members of the apolipoprotein family, were diminished in the livers of mice when HDBPL was depleted using RNA interference. As a result, the study animals exhibited decreased levels of non-esterified fatty acids, plasma triglycerides, and very low density lipoprotein. An elevation in the amount of HDLP was also associated with an elevation in ApoB levels in obese mice (Mobin et al., 2016).

A striking example of a membrane protein in which structural studies have provided mechanistic insight is polynucleotide phosphorylase (PNPase). This enzyme has been shown to be involved in the processing and degradation of mRNA in bacteria, plants (Yehudai-Resheff et al., 2007), and animals (Sarkar and Fisher, 2006). In humans, PNPase is primarily located within the mitochondrial intermembrane space (Chen et al., 2006; Rainey et al., 2006). It acts as a 3′-to-5′ endonuclease that degrades specific mRNA and miRNA targets thereby regulating multiple physiological processes (Lin et al., 2012). The X-ray crystallography structure of PNPase at 2.1 Å resolution (PDB entry: 3GCM) shows that the KH domain interacts with a long 3′ RNA tail. The hexameric ring-like structure of human PNPase is capped with a trimeric KH pore that is used to trap and deliver specific mRNAs and miRNAs for degradation (Lin et al., 2012).

Another multi-KH domain-containing protein, Scp160, was identified as having a significant role in the cell morphology of *Saccharomyces cerevisiae*. Scp160 deficient mutant strains were demonstrated to have increased cell size and DNA content (Wintersberger et al., 1995). Scp160 has fourteen KH domains that contribute to specific interactions with target mRNAs, particularly those encoding cell wall proteins (Hogan et al., 2008). Experimentally-derived 3D structures do not yet exist for any of these KH domains, nor is it known how they interact with their target NA. As summarized in Table 1, Scp160 appears to be enriched around the nuclear envelope (Wintersberger et al., 1995), with another study demonstrating co-fractionation of Scp160 with membrane pellets (Weber et al., 1997).

Membrane-associated prokaryotic KH domain proteins

The prokaryotic ortholog of the aforementioned PNPase protein is localized at the cytoplasmic face of the membrane of Gram-positive bacteria as a part of an RNA degradosome complex that is tethered to the integral membrane protein RNase Y (Cho, 2017). PNPase has a catalytic core at the N-terminus and RNA-binding KH-S1 domain at the C-terminus (Wong et al., 2013). Although ablation of the KH domain does not eliminate the protein's enzymatic activity, it dramatically reduces its RNA-binding activity and results in inefficient enzymatic turnover of mRNA (Stickney et al., 2005). Post-transcriptional regulation in bacteria allows them to respond quickly to environmental challenges. As a result, strains lacking PNPase are more susceptible to cold shock and other stressors (Yamanaka and Inouye, 2001).

The KH domain protein RNase Y is another bacterial endoribonuclease shown to play a role in the initial stages of mRNA degradation in many bacteria including *Bacillus subtilis*, *Streptococcus pyogenes*, and *Escherichia coli* (Chen et al., 2013a; Shahbabian et al., 2009; Baek et al., 2019). RNase Y is the major enzyme responsible for mRNA degradation in many Gram-positive bacteria and as such is essential for efficient translation due to its roles in primary transcript processing and targeted degradation of excess transcripts (Obana et al., 2016). The N-terminus of RNase Y is thought to interact with several protein partners including endoribonucleases, helicases, and enolases inside the RNA degradosome complex (Morellet et al., 2022; Commichau et al., 2009; Lehnik-Habrink et al., 2011) (see Fig. 4). RNase Y has the following structural arrangement: an N-terminal transmembrane domain followed by two helices that connect to the RNA-binding KH domain, a catalytically active phosphohydrolase (HD) module, and a C-terminal region of unknown function. It is assumed that the C-terminal region, together with the N-terminal coiled-coil structure, is important for RNase Y dimerization (Morellet et al., 2022). The single KH domain binding surface of RNase Y can accommodate only four consecutive RNA nucleotides. Because RNase Y depletion considerably enhances the half-life of bulk mRNA (Shahbabian et al., 2009), it appears to have relatively broad substrate specificity and interact with a wide variety of transcripts. In *B. subtilis*. RNase Y is localized to the inner surface of the cytoplasmic membrane where it has been visualized within dynamic short-lived foci (Hamouche et al., 2020). RNase Y is tethered to the membrane via a single pass N-terminal helix and is also known to form dimers as determined by NMR (Morellet et al., 2022), but no structural studies have yet been reported regarding binding of its KH domain to cognate RNA.

HofQ is a secretin protein (PDB: 2Y3M) that forms a channel through the outer membrane of *E. coli* and is responsible for internalization of extracellular DNA (Tarry et al., 2011) (see Fig. 4). In other organisms, including *Hemophilus influenzae*, the protein is known as ComE because it is involved in genetic competence and located downstream of the comABCD locus (Jorth and Whiteley, 2012). A ComE homolog of HofQ is also present in the Gram-negative periodontal pathogen *Aggegatibacter actinomycetemcomitans* (Jorth and Whiteley, 2012; Maughan and Redfield, 2009). The structure of *E.coli* HofQ reveals two secretin-like folds, the first of which is formed by means of a domain swap (Tarry et al., 2011). X-ray crystallographic analysis of the protein's extramembranous domain displays extensive structural similarity to other KH domains, including the presence of a GXXG motif consistent with a NA-binding function (Tarry et al., 2011). An *E. coli* mutant with a defect in *hofQ* is out-competed by the wild-type strain during growth, and is unable to utilize DNA as a sole carbon or energy source despite retaining the ability to be artificially-induced to competence (Palchevskiy and Finkel, 2006; Finkel and Kolter, 2001). These findings reveal distinct

mechanisms in *E. coli* for DNA uptake for nutrient acquisition as compared to genetic transformation. When DNA was supplied as the sole nitrogen source for *E. coli*, *hofQ* expression was increased. Surprisingly however, its expression was also elevated when alternative nitrogen sources were present suggesting that DNA is used once a sufficiently high concentration is present (Huang et al., 2022).

Era is a ubiquitous and functionally important ribosome biogenesis factor. It is necessary in *E. coli* as well as in mitochondria thus implying a bacterial origin (Gruffaz and Smirnov, 2023). A 2.4 Å crystal structure of Era has been solved (PDB:1EGA) and the protein has been shown to form dimers with a traditional KH type domain at the C-terminus (Chen et al., 1999). Era's N-terminal GTPase domain binds guanosine nucleotides and likely works as a molecular switch that is triggered by GTP hydrolysis and is reset by GDP/GTP exchange (Paduch et al., 2001; Sullivan et al., 2000). The C-terminal KH domain confers RNA-binding activity and is responsible for the association of Era with ribosomes (Johnstone et al., 1999). The KH domain interacts with the 3′-minor domain of small subunit ribosomal rRNA *via* a typical GXXG motif that recognizes a conserved GAUCA sequence (Hang and Zhao, 2003). Era is required for proper cell growth and division in *E. coli* (Gollop and March, 1991a; March et al., 1988). Specifically, when Era is depleted, *E. coli* stops multiplying, becomes increasingly elongated, and eventually lyses. The filamentous cells lack septa, but have correctly segregated nucleoids indicating a division failure unrelated to DNA replication (Gollop and March, 1991a). Overexpression, or hypermorphic alleles, of *ftsZ* suppress the filamentation of *E.coli* cells suggesting that a defect in FtsZ-mediated Z-ring formation may underlie the Era-associated cell division phenotype (Zhou et al., 2020). Immunoelectron microscopy investigations show that Era is located on or near the internal surface of the inner membrane, as would be expected for a membrane-signaling protein (Gollop and March, 1991b). Furthermore, Era appears in patches that may correspond to places with possible septation locations (Gollop and March, 1991b). The *Mycobacterium tuberculosis* Era ortholog, MRA_2388, is a recognized cell envelope-localized protein that interacts with several envelope proteins *of M. tuberculosis* (Agarwal et al., 2022). Era is essential in several bacteria including *Salmonella enterica* (Anderson et al., 1996) and *Haemophilus influenzae* (Akerley et al., 2002). In organisms in which it is not essential, e.g., in *Staphylococcus aureus*, *S. pneumoniae*, *M. tuberculosis*, and some *B. subtilis* strains, its loss is often associated with severe pleiotropic phenotypes (Wood et al., 2019; Minkovsky et al., 2002; Zalacain et al., 2003). A *Listeria monocytogenes* Era mutant having a truncated KH domain demonstrated poor adhesion to inert surfaces (Auvray et al., 2007). Numerous studies have shown that Era-deficient bacteria are vulnerable to both abiotic and biotic stressors (Lu and Inouye, 1998; Huang et al., 2007; Pillutla et al., 1995). In the cyanobacterium *Synechococcus elongate*, a KH domain-truncated Era mutant demonstrated overall increased lipid content and altered proportions of different lipid categories including hydrocarbons and specific fatty acids (Voshol et al., 2015).

Lastly, there is increasing evidence that the KhpA and KhpB KH domain proteins found primarily, but not exclusively, in Gram-positive bacteria are also membrane-associated. KhpB of *Helicobacter pylori* was shown to bind to and inhibit the HP0525 inner membrane ATPase, a component of the organism's type IV secretion system (Hare et al., 2007). The KhpB ortholog from *Streptococcus mutans* was found to be associated with a YidC-family protein member that is involved in integral membrane protein insertion. The KhpA and KhpB proteins are discussed in greater detail in a subsequent section.

Eukaryotic KH domain proteins

A prevailing theme that emerges from studies of KH domain proteins in eukaryotic organisms is that they play significant roles in embryogenesis and development processes. Consequently, abnormalities in this group of proteins leads to a host of physical and mental development problems, as well as several different types of cancers (Chopra et al., 2021; Dowdle et al., 2019; Weller et al., 2021; Gallardo et al., 2015). While the functional significance of a number of KH domain proteins is currently recognized, the underlying structural basis of associated disease phenotypes is poorly understood.

Involvement of KH domain proteins in development and cancer

The female germline-specific tumor suppressor protein GLD-1 contains an RNA-binding KH domain that is essential for oocyte development in *Caenorhabditis elegans*. This protein functions primarily during female germ cell development suggesting that it likely controls the expression of a selective group of maternal mRNAs (Doh et al., 2013). Null mutation of the encoding gene causes defective oogenesis and results in a tumorous germline phenotype (Jones et al., 1996). Bicaudal-C (Bicc1) is a conserved embryonic RNA-binding protein with three KH domains that regulates *Drosophila* development by binding to the 3′ UTRs of target mRNAs thereby reducing their stability and repressing their translation (Dowdle et al., 2022). Maternal knockdown and rescue experiments in *Drosophila* have demonstrated that KH domains of Bicc1 are required to regulate embryogenesis (Dowdle et al., 2019). Studies of Bicc1 mutants have revealed that KH2 is critical for RNA binding both *in vivo* and *in vitro*, whereas the KH1 and KH3 domains appear to play relatively minor roles. In the case of the human DEAD-box helicase DDX43 mentioned previously, mutational analysis has shown that the GXXG motif within its KH domain is involved in pyrimidine binding (Yadav et al., 2021). While DDX43 expression is low or undetectable in normal tissue, it is overexpressed in many tumors and represents another example of a potential target molecule for cancer therapy (Singh et al., 2022).

The PSC marker Developmental Pluripotency Associated 5 (DPPA5) protein contains an atypical KH domain that plays an important role in human Pluripotent Stem Cell (hPSC) self-renewal and cell reprogramming (Qian et al., 2016). Dppa5 overexpression improves the functional activity of hematopoietic stem cells (HSCs), while downregulation of Dppa5 profoundly impairs long-term reconstitution of HSCs (Miharada et al., 2014). In human FUBP1 (Far Upstream Element-Binding Protein 1), its ssNA interaction function is mediated by four tandem KH motifs (Ni et al., 2020). Deletion of the gene encoding FUBP1 is included within the 1p/19q co-deletion mutation, the main known cause of a form of primary brain tumor called oligodendroglioma (Weller et al., 2021). Another example of a KH domain protein associated with human malignancy is KHSRP (KH-type Splicing Regulatory Protein), which is involved in non-small cell lung cancer metastasis and has been suggested as a prognostic marker and novel therapeutic target for treatment of metastatic lung cancer metastasis (Yan et al., 2019). Thus, a number of examples have now been identified in which KH domain proteins are critical for developmental processes and are also associated with tumorigenesis when disrupted.

Insulin-like Growth Factor 2 mRNA-Binding Proteins (IGF2BPs) represent additional examples of human KH domain proteins that are important post-transcriptional drivers of cancer progression (Cleynen et al., 2007; Ioannidis et al., 2003; Köbel et al., 2007; Hammer et al., 2005; Ross et al., 2001; Zheng et al., 2008; Findeis-Hosey et al., 2010). They are predominantly expressed during embryonic development, but IGF2BP1 and IGF2BP3 are both re-expressed in a variety of aggressive cancers. Furthermore, they are strongly linked to cancer metastasis and production of oncogenic factors. IGF2BPs are necessary for appropriate nerve cell migration and morphological development, which likely involves control of cytoskeletal remodeling and dynamics, respectively. Mammalian IGF2BP paralogs have two RNA-recognition motifs (RRM) and four KH domains. These KH domains were reported to be essential for RNA binding *in vitro* and to interact with other RNA-binding proteins (Wächter et al., 2013). Evidence suggests that IGF2BP's interaction with target transcripts increases their half-life and leads to formation of an mRNA-protein complex around the nucleus (Dai et al., 2011). In humans, the MEX3 (Muscle EXcess) protein family consists of four

members, MEX3A through D. MEX3 proteins are distinguished by two KH domains that mediate RNA binding, and a C-terminal ubiquitin ligase domain. MEX3 proteins affect RNA fate *via* mRNA ubiquitination, and protein fate *via* protein ubiquitination. MEX3 paralogs show oncofetal expression, are significantly downregulated postnatally, and are re-expressed in a variety of cancers (Lederer et al., 2021). Neuron specific splicing factor proteins NOVA1 and NOVA2 are produced exclusively in the central nervous system. Each carries three KH-type RNA binding domains, but these are atypical in their RNA recognition since *in vitro* RNA selection and X-ray crystallography experiments have shown that they bind directly to pre-mRNA sequences having YCAY motifs to assemble the spliceosome (Saito et al., 2016). Lastly, members of the Poly(C)-Binding Protein (PCBP) family, PCBP1 and PCBP2, each contain 3 KH domains. PCBP1 and PCBP2 bind highly oxidized RNA, but exert opposing effects- either inhibiting or promoting apoptosis under oxidative circumstances (Ishii et al., 2020).

KH domain proteins in plants and fungi

StKRBP1 (*Solanum tuberosum* K-homology RNA Binding Protein 1) is a KH domain protein in potato plants that was identified as a susceptibility factor for potato blight (Wang et al., 2015). Another plant protein, ESR1 (Enhanced Stress Response 1), an *Arabidopsis* KH-domain protein, participates in plant hormone jasmonic acid signaling pathway and contributes to plant stress resistance (Thatcher et al., 2015). Another example in the model plant *Arabidopsis* is Rcf3, a putative RNA-binding protein with a KH domain that is required for heat stress-responsive gene regulation and thermotolerance (Guan et al., 2013). In addition, *Arabidopsis* HOS5 (High Osmotic Stress Gene Expression 5) is a KH-domain RNA-binding protein necessary for stress gene regulation and stress tolerance (Chen et al., 2013b). Furthermore, plant flowering time is regulated by the KH domain protein-FLOWERING LOCUS Y (FLY). Under long-night and short-day growing conditions a *fly1* knockout mutant, and a FLY artificial microRNA knockdown line, flowered earlier than the wild type (Dai et al., 2020). Yet another study demonstrated that HEN4-like (MdKRBP4), a KH domain-containing protein in apple, is involved in the plant's immune response (Wang et al., 2022).

An additional example of the ubiquity and importance of KH domain proteins, this time in the fungal kingdom, is the tandem KH domains of Khd4 protein from the pathogenic fungus *Ustilago maydis*. This protein recognizes AUACCC at the 3′ UTR of target mRNAs and is essential for regulation of morphology as well as pathogenicity in this organism (Vollmeister et al., 2009). Studies in another yeast species, *Schizosaccharomyces pombe*, showed that the multi-KH domain eukaryotic protein Rnc1 is subject to MAP-kinase-dependent phosphorylation (Prieto-Ruiz et al., 2020). Rnc1 deletion caused reduced cell length and an altered response to thermal stress due to binding to and destabilization of mRNAs encoding MAPK (Mitogen Activated Protein Kinase) activators Wak1 and Wis1, as well as mRNAs encoding negative regulators of the Atf transcription factor and Pyp1 and Pyp2 tyrosine phosphatases. Intriguingly, several prokaryotic KH domain-containing proteins are also linked to cell morphology. Thus KH domain proteins can influence coordinate regulation of complex and evolutionarily conserved signal transduction cascades.

KH domain proteins in prokaryotes

Most known KH domains within prokaryotic proteins are of the Type II category that are characterized by additional alpha helix and beta sheets at the N-terminal side of the domain (see Fig. 1). To date several KH domain proteins have been identified with varying roles in bacterial physiology and pathogenicity, and more examples are likely to follow. While KH domain-containing proteins in eukaryotes are frequently involved in cellular signaling, morphological development and oncogenesis, in prokaryotes this family of proteins is often associated with stress tolerance, membrane biogenesis, and cell division.

KhpA, KhpB, and other significant prokaryotic KH domain proteins

To date, the two best characterized KH domain proteins in prokaryotes are KhpA and KhpB. KhpA is a small protein containing a single KH domain that was first identified in *Streptococcus pneumoniae* as a protein involved in cell elongation (Zheng et al., 2017). KhpA and KhpB proteins in this and other organisms can homodimerize, or form heterodimers that results in expanded RNA-binding specificities (Zhu et al., 2023; Olejniczak et al., 2022; Zheng et al., 2017; Winther et al., 2019; Lamm-Schmidt et al., 2021). The gene encoding KhpB (also denoted *jag* or *eloR*) was first identified as being adjacent to the *spoIIIJ* gene sporulation gene in *B. subtilis* and was later shown to be involved in *S. pneumoniae* cell division (Zheng et al., 2017; Stamsås et al., 2017). The *jag* nomenclature stems from *spoIIIJ*-associated gene (Errington et al., 1992). SpoIIIJ is a homolog of the YidC family of bacterial membrane-localized chaperone/insertases (Saller et al., 2009), which function in concert with the SecYEG translocon and/or the signal recognition particle (SRP) pathway to insert integral membrane proteins during co-translational protein translocation (Mishra et al., 2019; Mishra and Jeannine Brady, 2021). YidC is part of a larger conserved family that also includes mitochondrial Oxa1 and Oxa2 (oxidative assembly) and chloroplast Alb3 (albino phenotype upon deletion) (Funes et al., 2009; Hennon et al., 2015). Bacteria such as Gram-negative species that have both an inner and outer membrane generally possess a single YidC localized to the inner membrane, whereas bacteria having a single membrane such as Gram-positive organisms generally possess dual YidC paralogs (eg. YidC1/YidC2, SpoIIIj/YqjG) integrated within the cytoplasmic membrane that demonstrate functional overlap as well as individual activities (Saller et al., 2009; Dong et al., 2008). The cariogenic dental pathogen *S. mutans* harbors orthologous copies of genes encoding KhpA (*smu_866*) and KhpB (*smu_338*). Genes encoding Jag/KhpB homologs are frequently found as part of an operon with *yidC1* (*spoIIIJ* in *B. subtilis*) and *rnpA*, which encodes the protein component of RNase P (Hansen et al., 1985) (Fig. 5A), whereas *yidC2* resides at a separate locus. Our investigation of the protein interactome of *S. mutans* YidC1 identified Jag as an interaction partner (Vasquez et al., 2021) (see Fig. 4). Again, this finding is consistent with the increasing observation that KH domain proteins are often associated with membrane-localized machineries.

In addition to its trademark KH domain, KhpB features a second RNA-binding domain, R3H, characterized by distinctive spacing of conserved R (arginine) and H (histidine) residues at the C-terminus. Schematic representations of *S. mutans* Smu_866 (KhpA) and Jag (KhpB) are illustrated in Fig. 5B. A Jag-N domain of unknown function is also found at the N-terminus of some KhpB orthologs. As a result, KhpB proteins can be divided into two groups: those containing both the Jag-N and R3H domains as well as the KH domain, and those with only the KH and R3H domains. Although the overall folding patterns of Jag-N, KH, and R3H domains of individual KhpB proteins are comparable, the primary sequence conservation of these domains within orthologous proteins appears to be low. As stated earlier, individual KH domains have relatively low RNA binding affinities. However, it is likely that stronger and more specific RNA binding by KH domain-containing proteins is accomplished by collaboration of multiple KH domains, possibly in concert with other RNA-binding domains such as the aforementioned R3H domain (Schneider et al., 2019; Korn et al., 2021).

According to a recent study, 48 % of the 45,555 bacterial species evaluated possessed KhpA, KhpB, or both (Olejniczak et al., 2022). The majority of identified organisms were Gram-positive, although Gram-negative examples such as *Fusobacteria* were found. An emerging theme regarding KhpA- and/or KhpB-containing species is that they usually lack the major RNA chaperone proteins Hfq and/or ProQ (Woodson et al., 2018; Olejniczak and Storz, 2017). Structure predictions of KhpA and KhpB from *S. pneumoniae* and *C. difficile*, using i-Tasser and ColabFold software, revealed a conformation typical of Type II KH proteins, namely an additional β-strand (β1) on the domain's N-

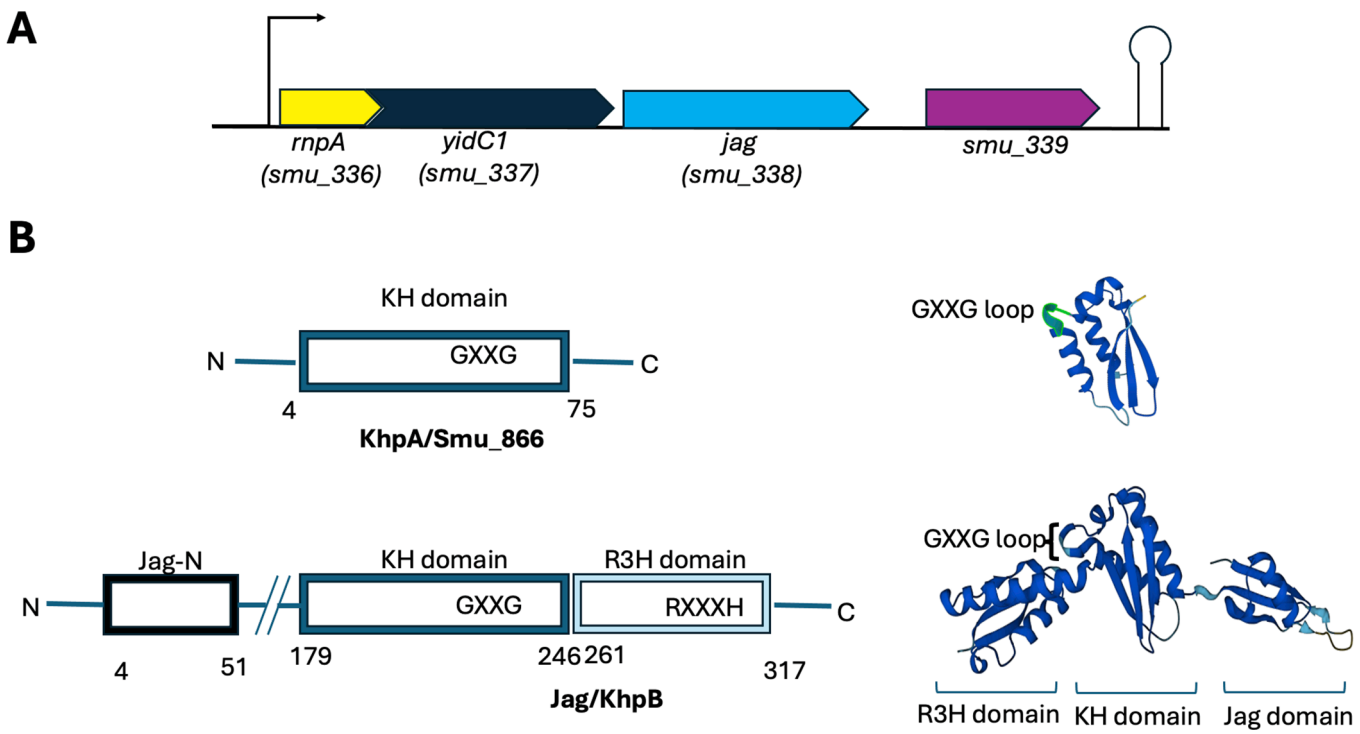

Fig. 5. Schematic representation of KH domain proteins from *Streptococcus mutans*. A. As is typical of Gram-positive organisms, the gene encoding Jag (homolog of KhpB) resides in an operon adjacent to the gene that encodes the chaperone/insertase paralog YidC1, and *rnpA* that encodes the protein subunit of RNase P. In *S. mutans*, a gene of unknown function, *smu_339,* is present downstream of *jag*. B. *S. mutans* Smu_866 (homolog of KhpA) and Jag are examples of KH domain proteins that do and do not possess the N-terminal Jag-N domain. Jag also contains an RNA-binding R3H domain at the C-terminus. Respective positions of the KH domain NA-binding GXXG motifs are indicated.

terminus that runs antiparallel to the first β-strand (β2) contained within the minimal core KH domain motif (Winther et al., 2019; Mirdita et al., 2022). RNA immunoprecipitation experiments in *S. pneumoniae* revealed that KhpA and KhpB bind a similar pool of approximately 170 RNA species composed of mRNAs, tRNAs and sRNAs (Zheng et al., 2017). However, in a study conducted by Lamm-Schmidt in *C. difficile*, ~1,400 RNAs comprised primarily of mRNAs co-purified with this bacterium's KhpB (Lamm-Schmidt et al., 2021). This represents a significantly greater number than reported to date in other species and suggests a variable range of KhpA and KhpB RNA targets in different organisms.

Other bacterial KH domain proteins of physiological significance

E. coli NusA is an RNA polymerase (RNAP) elongation complex component involved in transcriptional elongation, termination, anti-termination, cold shock, and stress-induced mutagenesis (Li et al., 2013). In solution, the NusA protein is often monomeric (Gill et al., 1991). Crystal structures of NusA from *M. tuberculosis* and *Thermotoga maritima* have been determined. In these organisms, the protein contains an N-terminal domain with an α3/β3 structure, an RNA-binding domain with an S1 region, and two KH domains joined by a flexible linker (Gopal et al., 2001; Shin et al., 2003). This structural organization facilitates the protein's simultaneous interactions with RNAP and nascent RNA transcripts. Similar to other cold shock proteins, the structure of the NusA-RNA complex from *M. tuberculosis* suggests that its NusA binds to nascent RNA structures and can act as an RNA chaperone (Beuth et al., 2005). Furthermore, in concert with the transcription factors Rho and NusG, NusA suppresses the expression of phage lambda or horizontally-acquired foreign genes, some of which may be harmful to the bacteria (Cardinale et al., 2008). In *E. coli*, NusA is required for stress-induced mutagenesis and promotes a distinct transcription-coupled repair mechanism highlighting NusA's direct contributions to multi-stress resistance (Cohen et al., 2010; Cohen and Walker, 2010).

The KH-like domain-containing Der GTPase of *E. coli* contains two tandem GTP-binding domains and has been linked to 50S ribosome subunit biogenesis (Hwang and Inouye, 2006). Homologs are highly conserved in prokaryotes, but not archaea or eukaryotes. Der over-expression has been shown to overcome growth impairment caused by abnormalities in the 23S ribosomal component of the 50S subunit (Hwang and Inouye, 2010). It has been proposed that the GTP-bound version of the *B. subtilis* Der ortholog, YphC, undergoes a major conformational shift thereby favoring interaction with negatively charged ribonucleic acids following exposure of its positively-charged high pI KH-like domain (Hwang and Inouye, 2008). This represents an example of cooperative interaction between KH domains and neighboring functional domains to influence NA-binding activities. Ribosome-binding factor A (RbfA) is a small ribosome assembly factor with a single KH domain that is involved in the development of the 30S subunit in *Thermus thermophilus* (Santorelli et al., 2021). Homologs of RbfA are found in most eubacteria and archaebacteria, as well as plant and algal chloroplasts and eukaryotic mitochondria (Rozanska et al., 2017; Rubin et al., 2003). The KH-domain of RbfA proteins represents a typical prokaryotic Type II domain. In *S. aureus*, RbfA binds to rRNA and has a KH-domain in which helices α2 and α3 (also denoted as a') create a helix-kink-helix (hkh) structure that contains a GXXG-like sequence motif (AXG) (Huang et al., 2003). Mitochondrial RbfA contains added C- and N-terminal extensions that provide important additional functional activities involved in the development of small ribosomal subunits (Hussain et al., 2016). In *E. coli*, RbfA is documented to be involved in the cold shock response (Jones and Inouye, 1996).

Contribution of KH domain proteins to bacterial cell division and morphology

The first recognition of the association of KH domain proteins with

bacterial cell division and morphology came from a study in which suppressor mutant screening of the growth defect associated with a P2BP (Penicillin Binding Protein) mutation in *S. pneumoniae* identified both KhpA and KhpB (Tsui et al., 2016). In addition, another study in *S. pneumonia* showed that KhpA and KhpB mutants each demonstrate smaller cell volumes (Ulrych et al., 2016). Speculation that KhpA and KhpB are involved in cell division was further reinforced by another observation in *S. pneumoniae* of a dispersed distribution of KH domain-containing proteins in non-dividing cells, followed by their co-localization at the mid-cell region of dividing cell (Zheng et al., 2017). Taken together, these reports suggest that KhpA and KhpB interact with each other during the cell division process. Indeed, subsequent studies employing bacterial two hybrid assays and pull-down experiments validated the interaction between KhpA and KhpB (Winther et al., 2019; Zheng et al., 2017). Additionally, *S. pneumoniae* KhpA and KhpB have both been documented to co-purify with *ftsA* mRNA which encodes a key cell division regulator in many prokaryotic species (Morrison et al., 2022; Zheng et al., 2017). In *S. pneumoniae*, the absence of KhpA and KhpB RNA-binding proteins leads to increased levels of transcripts of the *WalRK* two-component system regulon (Zheng et al., 2017), which responds to peptidoglycan stress during cell wall reorganization and coordinates cell wall metabolism with cell division (Dobihal et al., 2019). Thus, multiple lines of evidence point to the importance of KhpA/KhpB in cell division and cell morphology of several bacterial species.

Roles of prokaryotic KH domain proteins in virulence and pathogenesis

Given their central contributions to key physiologic process in most prokaryotes, it is likely that KH domain proteins also play significant roles in the production/regulation of virulence factors. A notable example thus far is in *Clostridium difficile* where KhpB alters toxin production by influencing the level of *tcdA* mRNA (Lamm-Schmidt et al., 2021). Comparison of the transcriptomes of wild-type and Δ*khpB* deletion strains of *C. difficile* suggests that KhpB can have either positive or negative effects on particular RNA levels (Lamm-Schmidt et al., 2021). This in turn likely leads to altered expression of additional genes relevant to toxin, or other virulence factor production highlighting the complexity of dissecting individual KH-domain protein-dependent pathways. In *S. pneumoniae* KhpB was identified as one of the genes that reduced fitness in a mouse model of pneumonia using a Tn-seq screen, thus suggesting its role in regulating virulence gene expression (van Opijnen and Camilli, 2012). In addition to DNA uptake, HofQ has also been linked to pathogenesis. For example in *Aggregatibacter actinomycetemcomitans*, which resides in multispecies biofilms in the subgingival pocket, HofQ is necessary for natural competence as well as virulence (Vahvelainen et al., 2023; Ahlstrand et al., 2018). Deletion of *hofQ* altered expression of genes linked to anaerobic growth, biofilm formation, and virulence resulting in decreased colonization and pathogenicity in a mouse model (Kulkarni et al., 2009; Vahvelainen et al., 2023). A *ΔhofQ* strain of uropathogenic *E. coli* showed a roughly 2-fold reduction in fluxing of bladder epithelial cells in mice (Kulkarni et al., 2009). In this system, the *ΔhofQ* strain demonstrated altered kidney colonization by day seven post-infection. In the oral pathogen *S. mutans*, the bacteria are heat-sensitive and grow poorly at 45 °C or under mildly acidic or high-osmolarity conditions when the KH domain protein Era is depleted (Sato et al., 1998; Baev et al., 1999), thereby suggesting poor performance under pathogenesis-relevant conditions. An *S. pneumoniae* Δera mutant has been reported to be attenuated in a murine respiratory tract infection model (Zalacain et al., 2003).

Another KH domain protein involved in bacterial virulence is CvfA, which is conserved among many bacterial species and contributes to expression of the *S. aureus agr* locus, a global virulence regulator that controls genes encoding a variety of exoproteins including hemolysin (Nagata et al., 2008). CvfA contains a transmembrane domain that anchors it to the bacterial membrane, an RNA-binding KH domain, and a metal-dependent phosphohydrolase domain (HD domain) (Nagata et al., 2008; Numata et al., 2014). In *S. pyogenes,* CvfA was shown to interact with enolase, a key glycolytic enzyme, implying that CvfA uses its KH domain to control transcript degradation rates of virulence factors, or their regulators, based on the nutritional status of the cell (Kang et al., 2010). Indeed, virulence of *S. pyogenes cvfA* mutants was greatly reduced in mice, demonstrating that CvfA-mediated post-transcriptional regulation, likely via endonucleolytic processing of mRNAs, contributes to pathogenesis (Kang et al., 2010).

An important aspect of bacterial pathogenesis is the capacity to respond to and endure environmental stressors, some of which are exerted by the host as defense mechanisms. Following such encounters, bacteria must degrade unwanted transcripts. As stated above, a key protein in this process is the exoribonuclease PNPase (Chen et al., 2016), which has a C-terminal RNA-binding KH domain involved in RNA processing (Cho, 2017). PNPase has been implicated as a virulence factor in several prevalent Gram-negative pathogens including *Salmonellae sp*., *Helicobacter pylori*, and *Yersinia sp*., where it typically impacts the type III secretion system (Rosenzweig and Chopra, 2013). A nonsense mutation within the gene encoding PNPase resulted in increased persistence of *Salmonella* in a murine model that was manifested by increased transcript levels of Salmonella Pathogenicity Island (SPI) genes (Clements et al., 2002). A mutagenesis screen also identified the previously characterized KH domain protein, RbfA, as one of the genes required for *Francisella tularensis* pathogenicity (Weiss et al., 2007). The KH domain protein RNase Y is ubiquitous among bacteria including those associated with pathogenesis, and plays a major role in virulence factor production. For example, *rny* deletion mutants of *S. aureus* exhibit reduced virulence in a murine bacteremia model, and the protein is required for the processing and stability of immature transcripts of the SaePQRS global virulence regulator system (Marincola et al., 2012). Furthermore, RNase Y is implicated in promoter-level activation of virulence gene expression that is thought to be mediated by short RNAs, some of which are degraded in an RNase Y-dependent manner (Marincola et al., 2012). RNase Y was also shown to be important in post-transcriptional processing of virulence-associated mRNAs of *S. pyogenes* including the rapid destruction of *rnpB* transcripts (Chen et al., 2013b).

The KH domain protein YbeY of *Vibrio cholerae* is crucial for virulence and stress regulation (Vercruysse et al., 2014). Mutant phenotypes include significantly reduced biofilm development and diminished cholera toxin (CT) production. Furthermore, the absence of YbeY renders *V. cholerae* highly sensitive to bile salts, antimicrobial compounds found in the small intestines of mammals and one of the first stress factors encountered by the bacterium after passing through the acidic stomach (Vercruysse et al., 2014). In *E. coli*, deletion of *ybeY* causes a pleiotropic stress phenotype, particularly heat stress (Davies et al., 2010). Additionally, YbeY stabilizes a type 3 secretion system transcript that supports injection of effector proteins across membranes into host cells and is necessary for virulence of enterohemorrhagic *E. coli* (McAteer et al., 2018).

Areas for future research

An area of significant interest for future research will be to expand our structural understanding of KH domain proteins and to better integrate structural and functional studies to achieve a more comprehensive understanding of known phenotypic consequences when such proteins are deleted or mutated. Post-translational modification of proteins, for example glycosylation, phosphorylation, methylation, ubiquitination etc., is a long-known mechanism for controlling their functional activities by modifying their physical/structural properties (Macek et al., 2019; Hu et al., 2006). However very few studies have examined the structure/function impact of post-translational modifications on proteins bearing KH domains, including of the KH domains themselves. IGF2BPs, Rnc1, and Jag are all examples of phosphorylated KH domain proteins (Dai et al., 2011; Prieto-Ruiz et al., 2020; Ulrych et al., 2016). More examples of post-translationally modified KH domain proteins are

likely to be discovered moving forward.

It is known that multiple KH domain proteins influence the fate of RNA transcripts with which they interact. Transcript stability can be increased or diminished depending on particular KH domain-mRNA combinations; however, how transcript half-life is modulated is not well understood. Whether KH domain proteins regulate their own production by interaction with their own transcripts or transcription/translation machineries is also an intriguing question. Our interest in KH domain proteins of *S. mutans* arose from the discovery that the KH domain protein Jag is among the protein interactome of the membrane protein insertase YidC1 (Mishra and Jeannine Brady, 2021). The significance of finding an RNA-binding protein in close proximity to a bacterial membrane protein insertase is unknown. One plausible explanation is a co-translational transport mechanism for certain YidC cargo proteins. Membrane-localized RNA-binding proteins have been described in mitochondria as key factors that chaperone specific RNAs *via* interaction with UTRs to orchestrate coupled translation/membrane protein insertion (Gerber et al., 2004; Gehrke et al., 2015; Ricart et al., 2002; Williams et al., 2014; Lesnik et al., 2014; Margeot et al., 2002). Whether KH domain proteins such as Jag function in a similar manner will be important to understand. Since KH domain proteins are capable of post-transcriptional regulation of other proteins by altering mRNA half-life, it is possible that bacterial KH domain proteins may impact *yidC* transcript stability or that of its substrates. Like Jag, many KH domain proteins are found as part of multi-molecular complexes including membrane-localized or membrane-associated proteins (Ginsberg et al., 2003; Wintersberger et al., 1995; Zheng et al., 2017; Hamouche et al., 2020). Membrane proteins represent a preponderance of potential therapeutic targets (Aguayo-Ortiz et al., 2021; Yin and Flynn, 2016), and comprise ~ 60 % of current drug targets (Young, 2023), highlighting the necessity of studying KH domain proteins in the context of membrane biology.

Given current evidence that KH domain proteins contribute to virulence regulation and pathogenesis in multiple infectious diseases, another area of future research will be antimicrobial development. The association of several key virulence phenotypes as related to KH domain interactions with particular NA targets, as well as the species distribution of certain KH domain proteins, suggests their utility as targets for directed antimicrobial therapeutic development. It will be important to continue to build on our structure/function knowledge base in pursuit of this goal. In addition to antimicrobial therapies, eukaryotic KH domain proteins are increasingly being recognized as promising targets for the development of cancer chemotherapeutics. As highlighted in this review, a variety of KH domain proteins are linked to the development of malignancies and neurodevelopmental disorders. Thus, one can anticipate that targeting KH domain proteins for anticancer treatment will be an expanding avenue in cancer research. Future work must also strive to expand current understanding of KH domain proteins by compiling a comprehensive library of KH domain structures, identifying their nucleic acid binding partners and characterizing the structural basis for the interactions, as well as by obtaining detailed information regarding their cellular locations and the biochemical pathways in which they participate. Experimentally-derived and computationally-predicted interactomes will allow researchers to better integrate and comprehend the significance of KH domain-containing proteins in a comprehensive spectrum of cellular processes. Lastly, future work should also address validation and continued characterization of previously identified or predicted KH domain interactions.

CRediT authorship contribution statement

Md Kamrul Hasan: Writing – review & editing, Writing – original draft. **L. Jeannine Brady:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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