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Biological Role of the 3β-Corner Structural Motif in Proteins

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Abstract: In this study, we analyze the occurrence of the unique structural motif, the 3β-corner, belonging to the Structural Classification of Proteins (SCOP) folds, in proteins of various origins. We further assess the structural and functional role of this motif as well as the clustering of the biological functions of proteins in which it occurs. It has been shown previously that the 3β-corner occurs with different probabilities in all beta proteins, alpha and beta proteins (α + β and α/β), and alpha classes occur most often in the composition of β-proteins. The 3β-corner is often found as a building block in protein structures, such as β-barrels, -sandwiches, and -sheets/-layers.

Keywords: 3β-corner; β-barrels; proteins

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1. Introduction

The 3β-corner was first discovered and described in 1992 [1]. It can be represented as a triple-stranded β-sheet folded onto itself so that the two β-hairpins are packed approximately orthogonally in different layers and the central strand bends by ~90° in a right-handed direction when passing from one β-layer to the other (Figure 1). All 3β-corners observed in proteins in different taxonomic groups, when viewed from their concave surfaces, are considered to be formed by Z-like β-sheets [1].

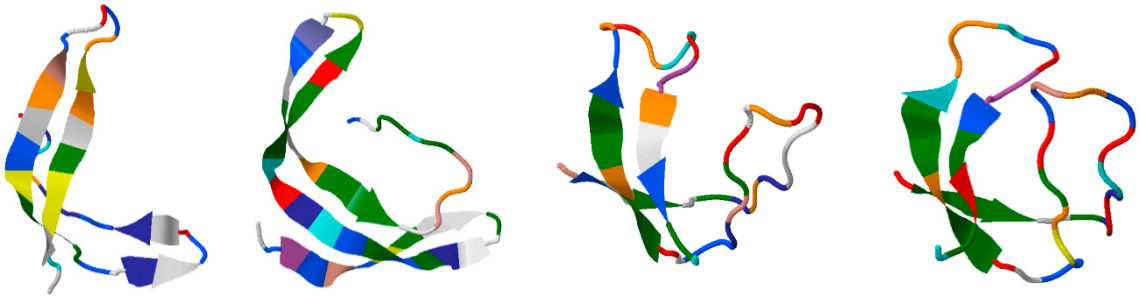
This motif has a unique and compact spatial fold and is often found in both homologous and non-homologous proteins. Certain small proteins are known to exist that consist only of 3β-corners and short irregular regions or one element of the secondary structure (PDB ID: 2F5K, 2A7Y, 1TXQ, etc.). The latter indicates that the 3β-corner motif (1) accepts a unique structure and can be a core around which the rest of the molecule or domain is folded and (2) is a stable structure in proteins.

We also found that the 3β-corner is often seen in proteins with β-barrels and is an integral part of the "barrel", accounting for 30–90% of the amino acid sequence and often acting as a key building block. In the latter case, the 3β-corner motif occurs typically two or more times in one "barrel".

The folds of β-barrels are extremely heterogeneous, with a total of 93 folds discovered to date, according to the Structural Classification of Proteins (SCOP). Barrels differ in terms of shear (S), ellipticity, and number of β-strands. The barrel structure itself can also be in either an open or closed conformation. It is likely that a wide variety of β-barrel folds arose as a result of divergent evolution, in particular with the duplication of genes encoding one β-hairpin [2]. These events resulted in proteins with similar structural arrangements but different biological functions.

The folds of β-barrels (n = 93) in the SCOP database (found at https://scop.berkeley.edu, accessed on 13 September 2022) are perhaps the most biologically significant and abundant in cytoplasmic and membrane proteins [3]. Barrels are composed of multiple β-strands (4–24) connected by loops and forming supersecondary β-hairpin structures.

β-hairpins, in addition to hydrophobic interactions, are stabilized by hydrogen bonds between adjacent β-strands in antiparallel/parallel orientations, thus forming β-sheets. The twisting of β-sheets forms a closed or open cylinder-like structure ("barrel" or "sandwich"). Membrane and cytoplasmic protein β-barrels differ in the amino acid composition and orientation of the hydrophobic amino acid residues, presented on a hydrophobic lipid bilayer for membrane proteins or oriented inside the hydrophobic core for soluble cytoplasmic proteins, respectively. Despite this, both types of β-barrels are characterized by similar geometry and structural arrangements. The multitude of scientific investigations focusing on the folds of β-barrels is also due to the wide range of biological functions attributed to the proteins in which they are found [3].



1	PDB ID	6H00:78–114	2R43:40–87	1SSH:4–46	1U06:4–47
2	Method	X-ray	X-ray	X-ray	X-ray
3	Resolution	1.66 Å	1.58 Å	1.40 Å	1.49 Å

Figure 1. Ribbon diagram representations of 3β-corners. Four examples of the tape model of the motif are presented. 3β-corners were extracted from pyridoxine 5-phophate oxidase (6H00), HIV-1 protease (2R43), SH3 domain from a s. cerevisiae (ISSH), and chicken alpha-spectrin SH3 domain (1U06) proteins. The coordinates of the 3β-corner in each protein (1), the experimental method for obtaining the structure (2), and the analysis resolution (less than 2Å) are indicated (3).

Most transmembrane β-barrels are found in a closed conformation and are characterized by their functions as pores or channels. The prominent representatives of these channel proteins include the outer membrane proteins (OMP) family [4]. In contrast, cytoplasmic β-barrels are represented by both open and closed structures in proteins that often exhibit a catalytic or ligand-binding function. Most OMPs contain an even number of β-strands (4–26) [5–7], while cytoplasmic, or soluble, forms of β-barrels are diverse and range from four to ten strands.

The characterization of 3β-corner motifs as a "building block" in β-barrel structures highlights their potential importance as part of the molecular basis of multifactorial pathologies accompanied by disturbances in metabolic processes and the suppression of the immune system. For instance, it is known that the development of amyloidosis is due to the formation of amyloid-β (Aβ) oligomers on the cell membrane. Furthermore, the phenomenon of fibril formation is considered a key process underlying neurotoxicity in Alzheimer's disease (AD). These oligomers are incorporated into the lipid bilayer in the form of pores and contain β-barrel structures [8,9].

It is also of interest to study β-barrel structures in viral proteins, for example, the non-structural protein-1 (Nsp1) of SARS-CoV-2. Efficient viral replication depends on the activity of Nsp1, a major virulence factor. The deletion or mutation of Nsp1 results in the attenuation of the viral infection in laboratory models and the restoration of the innate immune response in infected cells. The Nsp1 protein may be an important pathogenic factor and has been proposed as a potential therapeutic target for the treatment of COVID-19 [10,11]. Notably, the N-terminal fragment of SARS-CoV Nsp1 is represented by a β-barrel structure [12].

In this study, to further analyze and characterize them, we extracted 12,852 3β-corners in β-barrel-like structures from the Protein Data Bank (PDB, https://www.rcsb.org/, accessed on 13 September 2022). A systematic analysis of the occurrence of 3β-corner in proteins of various origins belonging to SCOP folds was performed. Subsequently, a cluster analysis of the biological functions of these proteins was performed. We believe that this study will help elucidate the diversity of β-folds in which the 3β-corner motif occurs and provide a much broader understanding of the role of the motif in various proteins.

2. Materials and Methods

While the overall spatial folding of the polypeptide chain is unchanged, the 3β-corner found in various proteins differs by the (1) length of β-strands, (2) the length and conformation of irregular sections connecting strands (turns, loops, bends), and (3) the conformation of the amino acid residues. These residues ensure the bending of the polypeptide chain by approximately ~90° and its transition from one β-layer to another with the formation of a right-handed supercoil. It has been shown that, at the points of transition from one β-layer to another, the polypeptide chain can acquire a β-bend conformation [13] or form any standard structure with a βαββ-, ββαLβ-, βαγβ-, βααγβ-, or βεβ-conformation [14]. In these structures, the γ-conformation corresponds to the region with angles $\varphi = (-90 \pm 30)^\circ$ and $\psi = (0 \pm 30)^\circ$ and the ε-conformation corresponds to the region with angles $\varphi = (110 \pm 30)^\circ$ and $\psi = (-170 \pm 20)^\circ$. Most often, these transition regions are occupied by Glycine (Gly) and sometimes by residues with small or flexible side chains [15].

A set of structures containing the 3β-corner was obtained using the 3D BLAST service (http://3d-blast.life.nctu.edu.tw/, accessed on 13 September 2022), which allows the identification of the correspondence of the structure in the scope dataset through geometric characteristics (Supplementary materials, Table S1).

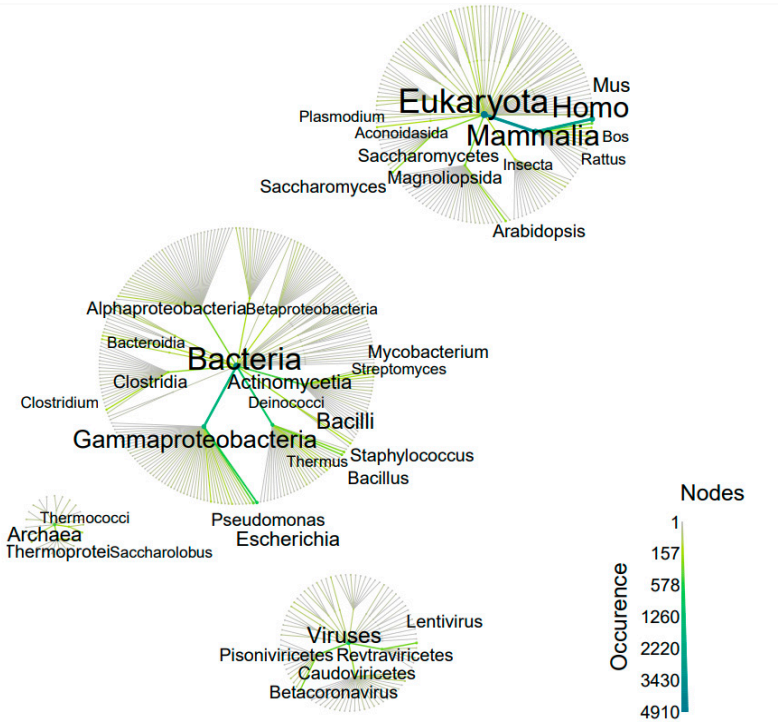
Data were analyzed using R version 4.2.1 (Vienna, Austria) [16]. To illustrate the distribution of protein fragments among different organisms, we constructed a heat tree, using the log(2) occurrence of the fragment in corresponding taxa and the R package Metacoder [17]. Fragments that could not be taxonomically identified were excluded from further analysis.

3. Results

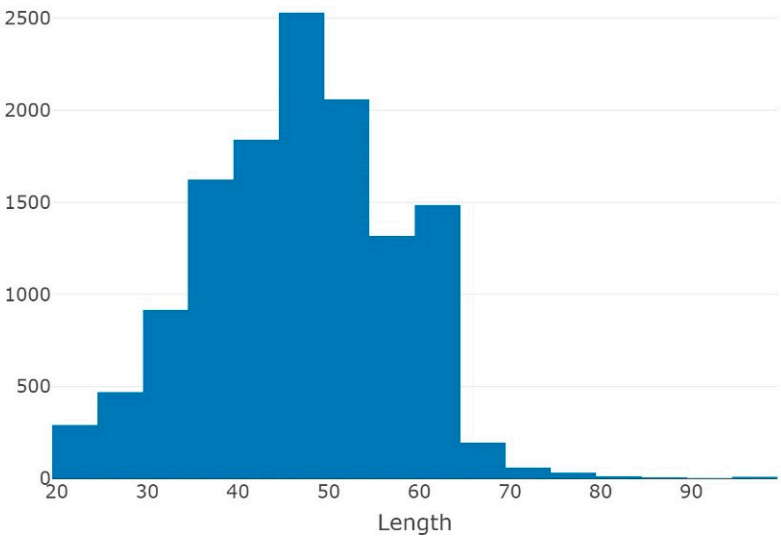
3.1. Occurrence of the 3β-Corner Motif in Proteins

Structural 3β-corner motifs were recognized and selected from the homologous and non-homologous proteins of various origins (Figure 2a). Most of these proteins belong to humans, other animals, and bacteria. There were also small groups of plant and viral proteins containing the motif. This observation is consistent with the diversity of annotated protein structures in the PDB. An analysis of the lengths of selected 3β-corners revealed that most structures are a length of 20–80 amino acid residues. The maximum distribution for the motifs falls within the range of 40–60 amino acids, with only a few of the studied motifs consisting of 70 or more amino acid residues (Figure 2b).

The structural motifs found and selected from various proteins also had a common spatial folding, unique to 3β-corners, although each may have their own characteristics and differences. For example, the structures can differ in the length of the β-strands, as well as the length and conformation of the irregular regions between the β-strands. Each β-strand is represented by five or more amino acid residues. Irregular sites connecting β-strands consist of two or more amino acid residues and have a conformation of turns, loops, or bends. All structures in this study retained chirality, and all the 3β-corners observed in proteins, when viewed from their concave surfaces, were considered to be formed by Z-like β-sheets.



(**a**)



(**b**)

Figure 2. (**a**) Origin of proteins in which 3β-corners have been identified. The taxonomic community is revealed by a heat tree map, showing the taxonomic context from higher ranks in the center to lower ranks in peripheries (kingdom to class). The abundance of species (occurrence) can be quantified and visualized by color and size of the nodes and edges. Graph components, such as the size and color of text, nodes, and edges, allow for the quantitative representation of multiple statistics simultaneously. Each node represents a taxon, and the edges determine where the taxon fits within the overall taxonomic hierarchy. Edge width is proportional to the number of taxa; (**b**) length distribution of 3β-corners in the examined dataset (n = 12,852, see Supplementary materials, Table S1).

3.2. Protein Type and Fold Diversity Containing 3β-Corners

The analysis of 3β-corner motif distribution among protein classes, including all alpha and all beta proteins, alpha and beta (a + b) proteins, alpha and beta (a/b) proteins, and other small proteins, revealed that most of the structures belong to the beta protein class (Figure 3). This class of proteins is characterized by the presence of structural domains in which the secondary structure consists entirely of β-sheets with the exception of individual isolated α-helices on the periphery. Prominent representatives are proteins containing the SH3 domain, the beta propeller, and the DNA-binding domain.

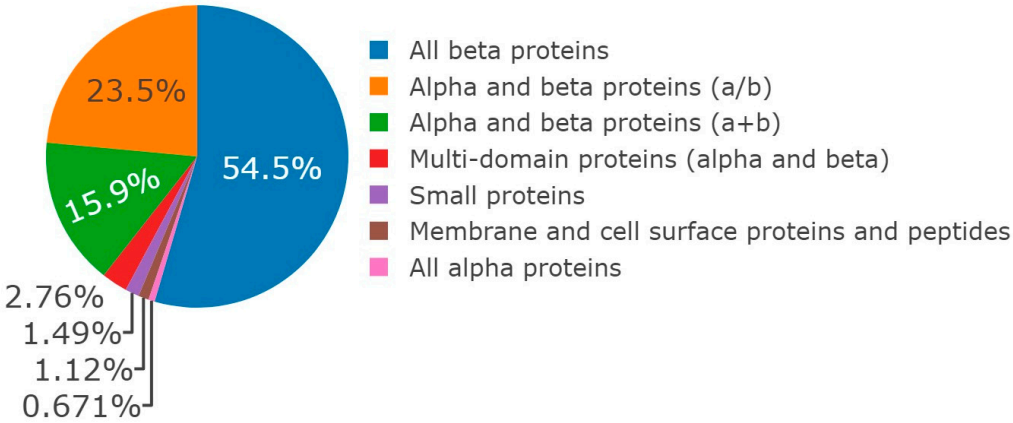


Figure 3. Histogram of the distribution of protein classes (all beta, all alpha, alpha + beta, alpha/beta) and SCOP folds within the study dataset.

To a lesser extent, the classes of mixed composition secondary structures (α + β) and (α/β) are represented within the dataset. α + β proteins are a class of structural domains in which the secondary structure consists of α-helices and β-strands arranged along the backbone in such a way that β-strands are oriented antiparallel to each other [18]. For example, proteins containing a ferredoxin domain, ribonuclease A, and an SH2 domain are included within this class. In contrast, α/β proteins are a class of structural domains in which the secondary structure consists of alternating α-helices and β-strands along the backbone. Thus, β-strands are mostly parallel to each other, seen in flavodoxin folds, TIM barrels, and leucine-rich repeat proteins, such as ribonuclease inhibitors [18]. The lowest occurrence of 3β-corner motifs was within the classes of small proteins (1.5%) and "all alpha" proteins (0.7%).

The occurrence of the 3β-corner motif in protein classes was determined by the frequency of β-strands, which for the "all beta" protein class was 54.5%, and for the (α + β) and (α/β) classes were 15.9% and 23.5%, respectively. Small proteins are an interesting study of folds, as their three-dimensional structure is represented by only one fold, indicating the autonomous stability of the motif. It also suggests that the motif may be an independent block, or "core", of folding.

After analyzing the distribution of 3β-corner motifs in different protein classes, we sought to understand β-barrel-like structures and what part of these structures is occupied by 3β-corners (Figure 4).

Figure 4 illustrates the distribution of amino acid sequence coverage attributed to the 3β-corner structural motif in SCOP structures containing the 3β-corner. As seen in Figure 4, the 3β-corner occupies anywhere from ~30–100% of these structure sequences. The maximum distribution falls between 50–70%.

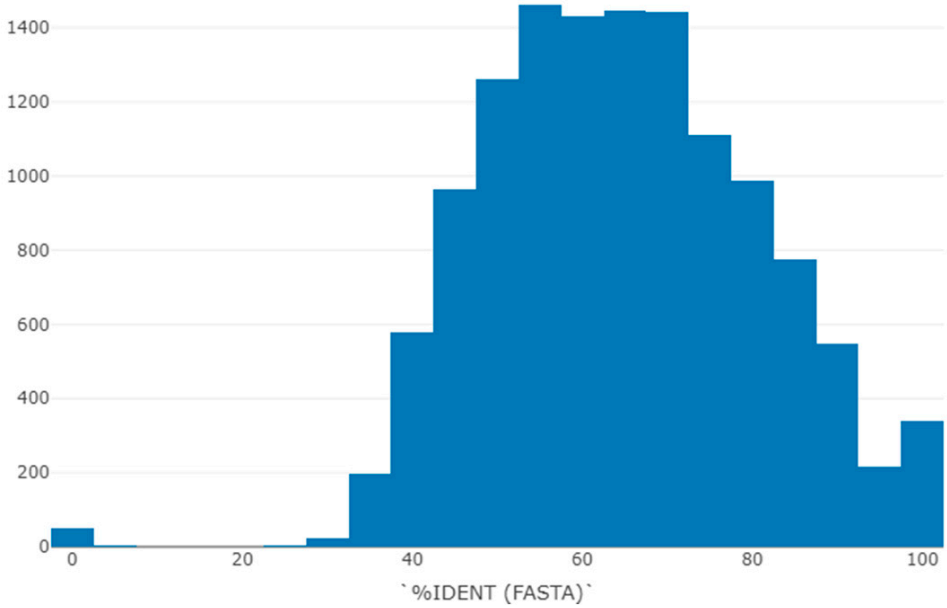


Figure 4. Histogram of the amount of amino acid sequence comprising the 3β-corner motif in SCOP fold structures containing the 3β-corner. The OX axis is the % of amino acid sequence, and OS is the number of structures.

We were also interested in the biological roles of proteins in which the 3β-corner structural motif was identified (Figure 5). Protein function was considered in terms of involvement in certain biological processes (BP), belonging to a particular cell compartment (CC), or being part of a molecular process (MF).

As seen in Figure 5, several binding functions are included within the top ten biological processes. Molecular partners in these binding functions include nucleotide-containing components (nucleotides, RNA/DNA, ATP), divalent cations (zinc, magnesium), as well as proteins with serine-type protease activity. Most of the proteins in this study's datasets are metal-binding proteins (15%), followed by proteins that bind nucleotide-containing biomolecules, such as ATP (12%), RNA (7%), DNA (6%) and free nucleotides (3%). In addition, a large portion are proteins that bind other protein partners (9%). The least represented are proteins that bind divalent zinc (5%) and magnesium (3%) cations, as well as components of supramolecular ribosome complexes (3%) and serine-type proteases, which can also be assigned to the group of binding proteins (4%).

For cellular localization, as expected, most of the proteins in our dataset were soluble cytosolic or cytoplasmic proteins (40%), extracellular proteins (11%), or involved in the composition of vesicles (5%) or, to a lesser extent, the plasma membrane (29%), etc.

The molecular functions of the proteins reflect their origin. Most were involved in the regulation of key processes of the cell cycle, transcription (6%), translation (3%), gene expression (2%), protein modification processes after synthesis (post-translational phosphorylation 2%), or metabolic transformations (3%). In addition, many were participants in the implementation of the innate immune response (3%).

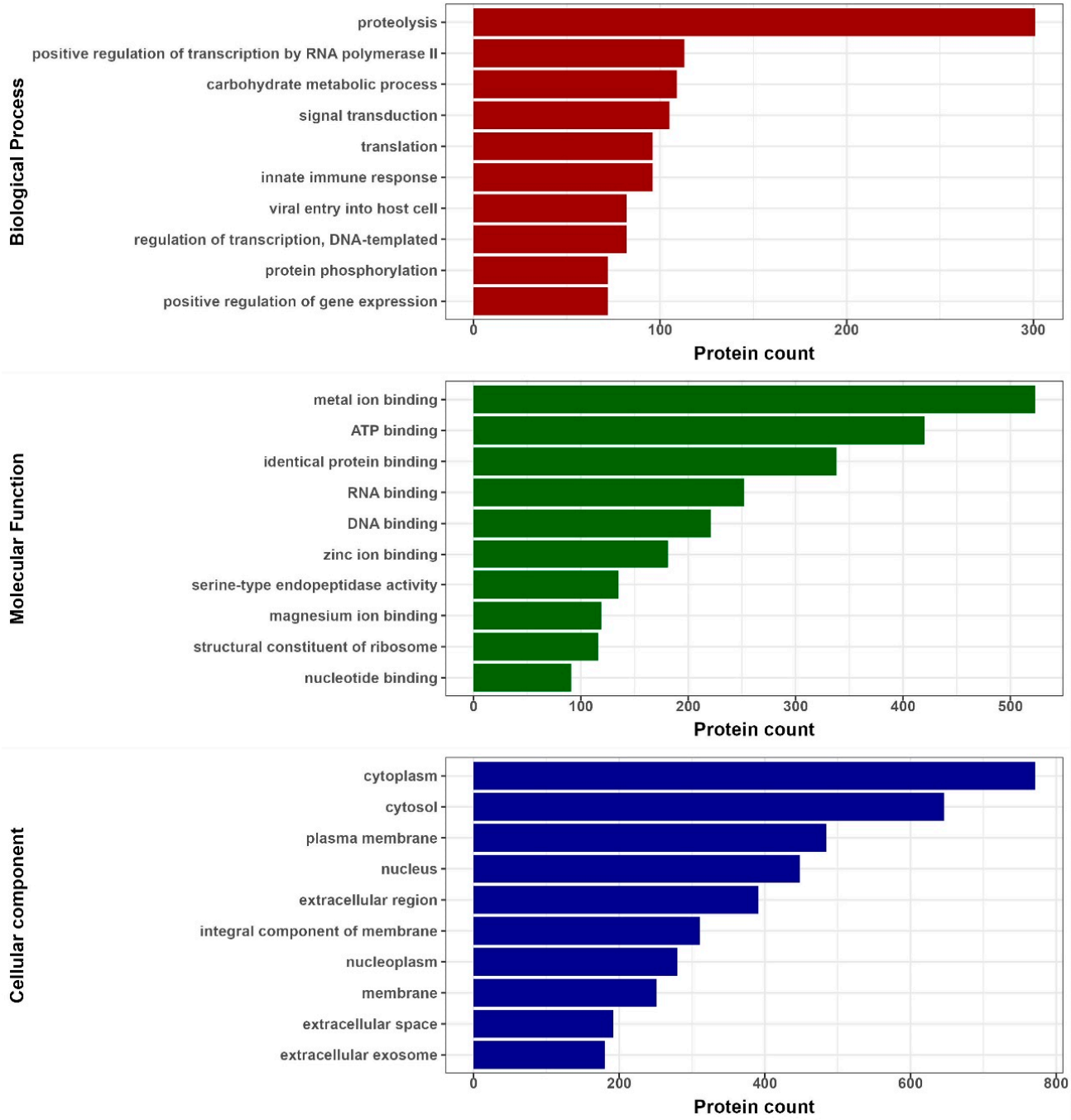


Figure 5. Biological functions of proteins in which the 3β-corner motif was identified. Green bars correspond to molecular processes (MF), red bars correspond to cell compartments (CC), and blue bars correspond to molecular functions (MF).

4. Discussion

We found 12,852 proteins containing 3beta corners in the Protein Data Bank (PDB). The high frequency of occurrence of the 3beta corners in unrelated proteins and the fact that many small proteins and domains merely consist of the 3beta corners suggests that they are relatively stable and can fold into unique structures per se. It can be concluded that the 3β-corners can act as nuclei or "ready-made" building blocks in protein folding. The larger protein structures can be obtained by the stepwise addition of other β-strands to the 3β-corner, taking into account a restricted set of rules inferred from the known principles of protein structure [14]. Molecular dynamics simulations also support these ideas [19].

The structural and biological roles of β-barrels are widely discussed in the literature and are primarily characterized as the components of cellular membrane proteins [3,20–22]. This is due to the structural similarity between the membrane proteins of prokaryotes (Gram-negative bacteria) and eukaryotic organelles (mitochondria and chloroplasts), which both contain barrel-like folds. These proteins perform important functions in the transport of biomolecules and cell signaling pathways and, furthermore, play a key role in membrane biogenesis. The diversity of protein structures containing barrel-like folds continues to increase [3]. However, little information is available in the literature on soluble proteins containing barrel-like folds, which are known to bind biomolecules (RNA, DNA, partner proteins, cations, etc.), such as enzymes. We thus aimed to explore different classes of proteins, which contain β-barrels and other structures with β-corner motifs, and their functions.

The main structural difference between water-soluble and membrane β-barrel-containing proteins is the orientation of their non-polar and polar amino acid residues [23]. In the case of water-soluble β-barrel proteins, hydrophobic residues are oriented inside the cylinder, which leads to the formation of a hydrophobic core, and polar residues are exposed on the surface of the cylinder and interact with the solvent. In contrast, in membrane β-barrel proteins, hydrophobic residues are oriented outward and interact with the surrounding lipid bilayer, while hydrophilic residues are oriented inside the cylinder, forming a pore. Soluble β-barrels sometimes contain a chromophore that determines their optical properties. These proteins bind and transport small hydrophobic molecules with high affinity (lipocalins), have superoxide anions in their active center, and are involved in cell signaling [24–26].

In this study, we noted that β-barrel-containing proteins were extremely important in the implementation of the cell cycle and that the "barrel" and "sandwich" and "beta-list" folds annotated in the SCOP database contain a unique structural motif called the 3β-corner. In the course of our study, we have seen that β-barrel structures are frequently occurring structures in various proteins and are most often present in proteins of the beta class (Figure 3). We have also shown that the 3β-corner structural motif, if found in a protein, is an integral part of these structures (Figure 4). However, the number of 3β-corner motifs in these structures can differ. There are structures containing one 3β-corner in their composition, while others may have several of them in one structure. Analyzing the selected set (12,852) of 3β-corner-containing β-barrels, we found that the 3β-corner, being an independent block or "core" of folding in small proteins, performs the same role in β-barrels.

The structural motifs of the 3β-corner type, having a unique spatial arrangement in their polypeptide chain, may be the hypothetical "embryos" in the process of folding and forming β-barrels. In these cases, the remaining parts of the peptide chain can be attached to the β-barrel structures in accordance with a few simple rules. In our studied set of proteins, the folds corresponding to the barrel (~30%) were equally divided into partially or completely open and closed conformations. The typical structure contains a small number of β-strands (n = 5) in the cylinder, whereas proteins with a barrel containing nine or more β-strands are less common. Partially closed and fully closed cylinders are characterized by a high shear factor (S = 8, 10), that is, a high ellipticity. Thus, they tend to be more spatially compact and resemble a flattened barrel in appearance.

Sandwich (~10%) and beta-sheet (~10%) folds are also well studied and in our dataset are formed mainly by a small number of β-strands (4 or 5). The difference in these folds is that the sandwich structures are formed by two β-sheets (five β-strands each), forming a kind of closed structure that also resembles a flattened barrel. It is likely that within the variety of folds of β-containing proteins, 3β-corners are not just the "building blocks" of structures like β-barrels but also play a more important role. That is, 3β-corners likely have structural and functional roles. This makes them an intriguing area of study.

In this study, we conducted a systematic analysis of the occurrence of 3β-corners in proteins from β, α, α + β, and α/β classes, as well as small proteins and those belonging to different SCOP folds. Our analysis showed that the 3β-corner is often found in structures of the β-barrel type, including "barrel", "sandwich", "β-sheet", and "layer" constructs. The 3β-corner was also found to be an "integral" part or "building block" of these structures. In α- and small-proteins, the 3β-corner structural motif is also included in the barrel. The 3β-corner was further recognized to be part of α/β-proteins, and thus it is likely also included in other types of structures that were not considered in this study. In these proteins, the β-corners were found in barrel or sandwich structures, and a small number of them in layer structures. Conversely, in α + β-proteins, the 3β-corners were equally likely to be a component of layer, barrel, or other types of structures, and a small number of them were found in sandwich and β-sheet structures.

When we investigated the biological processes in which proteins of the selected dataset were involved, we observed that most were involved in the binding and transport of biological molecules, primarily nucleotide-containing, and divalent cations (Figure 5).

Almost all vital processes of cell ontogenesis were also carried out with the participation of these types of proteins, potentially suggesting an important biological role and significance of β-corner-containing structures (Supplementary materials, Table S2). The most numerous groups of proteins containing the structural motif under study are participants in the biological processes of proteolysis (neutrophil elastase, prothrombin, coagulation factor XI, cathepsin G, etc.), the regulation of transcription (general transcription factors IIF and IIE, transcription initiation factor IIA, CCAAT/enhancer-binding protein beta etc.), signal transduction (zinc finger CCCH-type with G patch domain-containing protein, general control transcription factor GCN4, tyro-sine-protein kinase Lck, integrin alpha-V), translation (50 S ribosomal protein L34, GTP cyclohydrolase 1, RNA-binding protein Hfq etc.), and innate immune response (neutrophil cytosol factor 2, toll-like receptor 5b, RNA helicase, immunoglobulin lambda constant 2 etc.).

The likely medical significance of proteins containing the 3β-corner in beta-propellers, beta-layers, barrels, etc., is also of great importance. (Table 1). Table 1 lists ten proteins that are involved in the pathogenesis of multifactorial diseases, such as cancer, diabetes mellitus, and neurodegenerative diseases. As can be seen from Table 1 and as mentioned earlier in this study, the 3β-corner motif is an integral and significant part of beta-containing structural folds (beta-propellers, beta-layers, barrels) and often makes up more than 80% of the amino acid sequence of these core folds. It also draws attention to the belonging of proteins to the class of all beta proteins and the mixed-in composition elements of the secondary structures alpha and beta proteins (a + b) and alpha and beta proteins (a/b) (Table 1).

Table 1. Examples of medically significant proteins whose three-dimensional structure contains the 3β-corner motif.

UniProt ID	Protein Name	PDB ID (Locus, a.a.)	SCOPE Fold	% Ident *	Core Fold	Disease **	Class of Protein	Ref.
P27487	Dipeptidyl peptidase 4	1R9N (402–446)	b.70	95.1	beta-propeller	Carbohydrate metabolic disorder, type 2 diabetes mellitus	All beta proteins	[27,28]
P02679	Fibrinogen gamma chain	3E1I (F242–279)	d.171	94.1	unusual fold	Congenital afibrinogenemia	Alpha and beta proteins (a + b)	[29,30]
P0DMV8	Heat shock 70 kDa protein 1A	1S3X (64–116)	c.55	93.9	beta-layer	Cancer	Alpha and beta proteins (a/b)	[31,32]

Table 1. *Cont.*

UniProt ID	Protein Name	PDB ID (Locus, a.a.)	SCOPE Fold	% Ident *	Core Fold	Disease **	Class of Protein	Ref.
P30405	Peptidyl-prolyl cis-trans isomerase F	4J5A (45–108)	b.62	95.0	barrel, closed	Neurodegenerative disease	All beta proteins	[33,34]
Q9Y3R4	Sialidase-2	2F24 (163–210)	b.68	93.2	beta-propeller	Glycoproteinosis	All beta proteins	[35]
P08514	Integrin, alpha 2b	3ZDY (218–272)	b.69	92.2	beta-propeller	Glanzmann's thrombasthenia	All beta proteins	[36]
Q12888	Tumor protein p53 binding protein 1	3LGF (1540–1584)	b.34	85.4	barrel, partly opened	Cancer	All beta proteins	[37,38]
Q14653	Interferon regulatory factor 3	1J2F (201–246)	b.26	85.2	sandwich	Autoimmune disease	All beta proteins	[39,40]
P05230	Fibroblast growth factor 1	3UD8 (19–60)	b.42	84.2	barrel, closed	Cancer	All beta proteins	[41,42]
P40337	E3 ubiquitin protein ligase	5NW2 (114–154)	b.3	83.8	sandwich	Hemangioma	All beta proteins	[43]

% Ident *—amount of amino acid sequence comprising the 3β-corner motif in SCOP fold structures containing the 3β-corner; Disease **—web resource that integrates evidence on disease–gene associations from automatic text mining, manually curated literature, cancer mutation data, and genome-wide association studies (score > 5; https://diseases.jensenlab.org/, accessed on 13 September 2022).

Interestingly, β-barrel-containing proteins are considered by researchers to be convenient models for creating proteins with desired properties, also known as mimetics. Four years ago, at the University of Washington, scientists created β-cylinder protein structures from scratch for the first time. A protein capable of binding to a small ligand molecule was then investigated. The ability to produce such proteins from scratch, or de novo, opens up new possibilities for scientists to create proteins that are different from those found in nature. These proteins can be specifically designed with high fidelity and affinity to bind to and act on specific, small-size targets. In these studies, the structure of the β-cylinder protein turned out to be ideal, as one end of the structure could be designed to stabilize the protein molecule and the other end could be used to create a cavity, the site of binding to the ligand molecule [44].

As part of the developing field of de novo protein engineering, a study published in 2021 by Anastassia Vorobieva and colleagues from the Department of Biochemistry at the University of Washington showed the design of a complex protein barrel motif with a given function that was successfully implemented [45]. Vorobieva et al. described the successful computational design of eight-strand transmembrane β-barrel (TMB) proteins. Among 23 calculated structures, two structures were experimentally confirmed using nuclear magnetic resonance and X-ray crystallography, which opens up further possibilities for individual pore design, including for single-molecule sequencing as part of molecular detectors. In this regard, our study can be considered an important new understanding of the organization of barrel-like structures, with implications for both fundamental and applied research.

5. Conclusions

As a whole, this study turns to proteins with well-known β-barrel-like structures but from a new angle. The importance of barrel-containing proteins in cell ontogeny cannot be understated, as these proteins participate in processes such as transcription, translation, gene expression, protein modification after synthesis, metabolic transformation, and the implementation of the innate immune response. The barrel-like structures contain the

3β-corner motif as an integral component, which is also compact, is characterized by a hydrophobic core, and is considered a germline structure in protein folding. The screening of more than 12,500 protein structures extracted from the PDB has shown that barrel-containing proteins are found not only in all beta classes but are also expressed to some extent in other known protein classes. The 3β-corner of known SCOP barrel-like folds makes up anywhere from 40–80% of the amino acid sequence, which indicates a structure-forming role for the motif. The development of modern computer design methods has now presented new possibilities for using these closed protein structures as mimetics.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pr10112159/s1, Table S1: Data on experimental PDB structures; Table S2: The biological role of the studied structures.

Author Contributions: Conceptualization, A.L.K. and L.I.K.; methodology, D.V.P. and V.R.R.; software, K.S.N. and D.V.P.; validation, A.A.S. and K.A.M.; data curation, V.R.R.; writing—original draft preparation, A.L.K., L.I.K. and V.R.R.; writing—review and editing, A.L.K., L.I.K. and K.A.M.; visualization, A.V.E.; project administration, A.L.K. All authors have read and agreed to the published version of the manuscript.

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