Chapter 8
Importance of Natural Proteins in Infectious Diseases

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Abstract Proteins are important biomolecules, extensively involved in almost all biological processes. A number of proteins are also implicated in infectious diseases. Bacterial proteins used in adhesion to host epithelium, bacterial toxins, and viral membrane glycoproteins are some of the proteins involved in infectious diseases. Even components of the host innate immune system like Toll-like receptors and Nod-like receptors and adaptive immune components like immunoglobulins aiding in defense against pathogens are important biological proteins. Chaperones like acid and heat shock proteins provide protection from high temperatures, metabolic poisons, and other stressful conditions. Several natural and artificial proteins are components of vaccines, a key strategy to control fatal diseases, lacking empirical treatment. It is necessary to investigate these proteins, to develop new biomedical tools and technologies, aiding in eradication of various diseases. Thus, further research should be carried out in this field, for saving and improving quality of human lives.

Keywords Toll-like receptors · Major histocompatibility complex · Immune response

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8.1 Introduction

An infectious disease is a disease that is caused by the invasion of a host by agents whose activities harm the host's tissues (that is, they cause disease) and can be transmitted to other individuals (that is, they are infectious). Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence, and growth of pathogenic biological agents in an individual host organism. Infections are caused by infectious agents such as viruses, and prions, microorganisms such as bacteria. Proteins might be involved in causing a disease as well as protecting the host from it. Various membrane proteins of microorganisms (virus, bacteria, parasites, etc.), prions are responsible for causing different diseases. Proteins like heat shock proteins/chaperons aid in causing as well as protecting from diseases. Proteins might also be involved in playing solely protective roles against infections like various cell surface receptor proteins (Toll-like receptors, Nod-like receptors, etc.), which trigger protective immune responses. Nowadays, various antimicrobial peptides or antibiotics are known to kill microorganisms or inhibit their growth, thus aiding in treatment of diseases.

Thus, proteins, one of the most incredible biomolecules, are extensively involved in almost all biological mechanisms, especially those implicated in pathophysiology of infectious diseases. The understanding of this topic is essential for developing different biomedical tools, for combating various diseases, thus, improving the quality of human life.

8.2 Bacterial Proteins

A number of bacterial proteins are involved in its pathogenesis and virulence. Bacterial infections are usually initiated by adherence of the microbe to a specific epithelial surface of the host, otherwise the organism will get removed: (1) Fimbrial adhesions involved in mediating attachment of some bacteria to mammalian cell surfaces, e.g., *Neisseria gonorrhoeae* use pilli to adhere to the mucous membrane of urethra and can resist the flushing action of urine [1, 2]. (2) Nonfimbrial adhesion including the filamentous hemagglutinin of *Bordetella pertussia* helping in attachment to respiratory epithelium, a mannose-resistant hemagglutinin produced by *Salmonella typhimurium* and a fibrillar hemagglutinin from *Helecobacter pylori* [3, 4]. Other adhesions like Protein F produced by *Streptococcus pyogenes*, aiding in attachment to pharyngeal epithelium [5]. Some extracellular bacterial proteins considered invasins like hyaluronidase, produced by *Streptococci, Staphylococci,* and *Clostridia*, which degrades hyaluronic acid of connective tissue [6, 7], collagenase produced by *Clostridium sp*, which dissolves collagen framework of muscles [8], neuraminidase produced by *Vibrio cholerae* and *Shigella dysenteriae*, which degrades neuraminic acid of intestinal

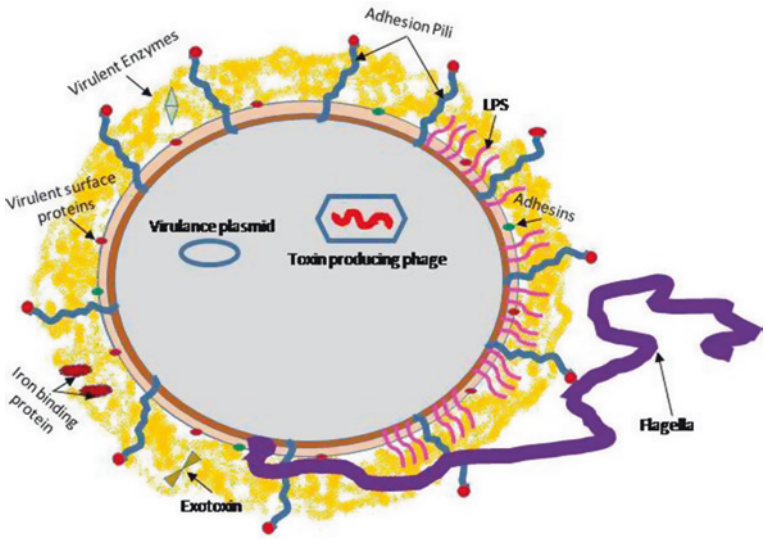

Fig. 8.1 Structure of bacteria

mucosa [9]. Other extracellular proteins like invasive enzymes, e.g., coagulase, contributes to the formation of fibrin walls around staphylococcal lesions [10]; exotoxins (proteins released extracellularly), like neurotoxin (Tetanus toxin, by *Clostridium tetani*, Botulinum toxin by *Clostridium botulinum*) [11] and cytotoxins (Diphtheria toxin produced by *Corynebacterium diptheriae*) [12, 13], also known as A-B toxins (consisting of 2 subunits: one binds to cell surface receptor and the other is transferred into the cell to damage the cell) [14], cytolytic toxins (attacking cell constituents causing lysis) like hemolysins produced by *Bordetella pertussis*, inducing apoptosis of host cells, super antigen toxins (e.g., superantigen, sized 22KDa produced by 5–25 % of *Staphylococcus aureus* isolates, causing toxic shock syndrome (TSS) by stimulating the release of large amounts of interleukin-1, interleukin-2 and tumor necrosis factor, etc.) [15]. Enterotoxins (exotoxins that act on the small intestine, generally causing massive secretion of fluid into the intestinal lumen, leading to vomiting and diarrhea) produced by *Vibrio cholerae, E. coli* O157:H7. Endotoxins (generally cell-bound toxins released only when cells are lysed) produced by most Gram-negative bacteria are generally non-proteinaceous, lipopolysaccharide in nature [16] (Fig. 8.1).

8.3 Viral Proteins

Viral glycoproteins, made up of carbohydrates and proteins mainly help in adherence of viruses to host cell surfaces and internalization of viral components. The

addition of sugar chains or glycosylation of the protein surface-components, can happen either at asparagine, and is termed *N*-glycosylation, or at hydroxylysine, hydroxyproline, serine, or threonine, and is termed *O*-glycosylation. Glycosylation is often present in proteins that are at least in part located in extracellular space. The sugar group can assist in protein folding or improve its stability. Glycoproteins also aid in immune cell recognition. Viral glycoproteins are composed of three parts: External/Ecto-domain, which interacts with host; Transmembrane segment, which spans the viral envelope membrane, typically α-helix; and Endo-domain, the internal part. Ecto-domain can be of two classes: Class I, found in Orthomyxoviruses, Paramyxoviruses, Retroviruses, Filoviruses and Coronaviruses; Class II, found in Flaviviruses and Alphaviruses. Other types of ecto-domains that do not fit in class I and II are Glycoprotein B (gB) of Herpes Simplex Virus (HSV) and Glycoprotein G of Vesicular Stomatitis Virus (VSV) [17–20].

Glycoproteins on the surface of viruses are anchored in the lipid bilayer of the envelope by means of hydrophobic bonds, and only about 30 amino acids penetrate into the virus. These transmembrane proteins have large external domains and small cytoplasmic domains. Viral glycoproteins are oligomers that are associated with each other to form tetramers, etc. There are often the spikes seen on the virus surface. Some glycoproteins such as the influenza hemagglutinin are anchored at both ends, thus forming a loop. In such cases a signal sequence at

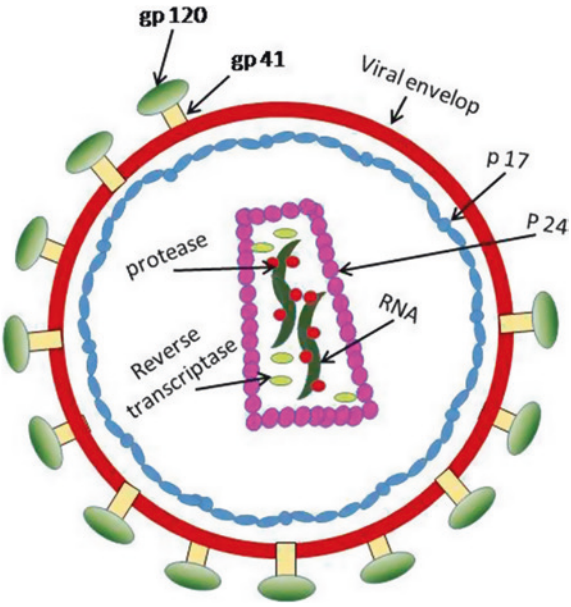

Fig. 8.2 Structure of human immunodeficiency virus (HIV)

the amino end has been removed. There are two types of glycoproteins: External glycoprotein anchored in the envelope by a single transmembrane domain, and a short internal tail. These proteins are usually the major antigens of the virus and involved in functions such as hemagglutination, receptor binding, and membrane fusion. The other classes are channel proteins, which are mostly hydrophobic proteins that form a protein lined channel through the envelope. This protein alters permeability of the membrane (e.g., ion channel). Such proteins are important in modifying the internal environment of the virus [21–24] (Fig. 8.2).

8.4 Toll-Like Receptors

The first line of defense against pathogenic microorganisms is innate immunity, and its activation is initiated by the recognition of microbial structures by pattern recognition receptors (PRRs). The first and most studied class of PRRs is that of a proteinaceous receptor named Toll-like receptors (TLRs), named after the Toll receptor of *Drosophila melanogaster*. Ten human TLRs have been identified, from TLR 1 through 10, with important roles in host defense against bacteria, viruses, and fungi [25, 26]. They recognize a large array of pathogen- associated molecular patterns (PAMPs), including peptidoglycan, lipoproteins, lipopeptides, phenol-soluble modulin, lipoteichoic acid, lipoarabinomannan, atypical lipopolysaccharides (LPSs), porins, flagellin, heat shock proteins (HSP), lycoinositol phospholipids, glycolipids, zymosan, also nucleic acids like double-stranded RNA of viruses, etc. [27, 28]. TLR family members are characterized structurally by the presence of a leucine-rich repeat (LRR) domain in their extracellular domain and a TIR (Toll/interleukin-1 receptor homology) domain in their intracellular region [29]. Expression of TLRs is modulated by a variety of factors such as microbial invasion, microbial components, and cytokines.

There are two distinct signaling pathways of TLRs: Myd88-dependent and Myd88-independent pathways. The MyD88-dependent pathway signals via MyD88, IRAK, and TRAF6 and leads to NF-κB activation. The activity of NF-κB (Nuclear Factor Kappa-light-chain-Enhancer of Activated B cells) is regulated by association with I-κB, which sequesters NF-κB in the cytoplasm until phosphorylated on serine residues by the I-κB kinase (IKK) complex. This phosphorylation leads to the dissociation and nuclear translocation of NF-κB. NF-κB is a transcription factor involved in upregulation of genes responsible for both the innate and adaptive immune responses, e.g., genes involved in T cell development, maturation, and proliferation, cell apoptosis, etc. Similarly, in the MyD88-independent pathway an adaptor molecule named TIR domain-containing adaptor protein (TIRAP)/MyD88- adaptor-like (Mal) is involved (Fig. 8.3).

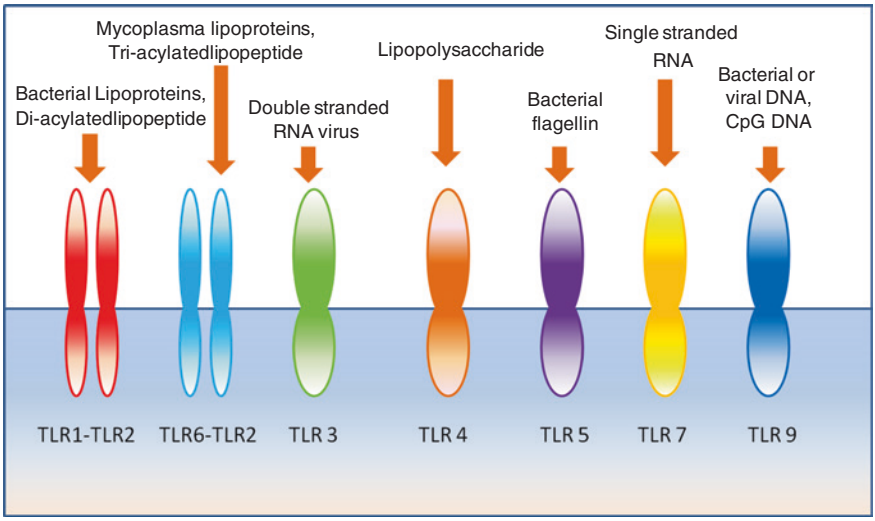

Fig. 8.3 Toll-like receptors

8.5 Nod-Like Receptors

Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are a group of evolutionarily conserved intracellular proteinaceous PRRs that play a vital role in innate immunity and host physiology, in both plants and animals [30, 31]. In humans there are 22 known NLRs, and the association of mutations and single nucleotide polymorphisms (SNPs) in their genes with human diseases reflect their vital role in host defense. NLRs also play important roles in reproduction and embryonic development. The characteristic feature of NLRs is a central NOD (or NACHT) domain, required for oligomerization, an *N*-terminal homotypic protein–protein interaction domain and a *C*-terminal series of leucine-rich repeats (LRRs) involved in agonist sensing or ligand binding [32].

Mammalian NLRs are subdivided into four subfamilies based on the variation in their *N*-terminal domain: NLRA or Class II transactivator (CIITA) contains an acid transactivation domain, NLRBs or neuronal apoptosis inhibitor proteins (NAIPs) possess a baculovirus inhibitor of apoptosis protein repeat (BIR), NLRCs have a caspase-recruitment domain (CARD), and NLRPs a pyrin domain (PYD). NLRX1 contains a CARD-related X effector domain. Among the NLRs, NLRP1, NLRP3, NLRP6, NLRP7, NLRP12, NLRC4, and NAIP have been reported to operate via inflammasomes. Other NLRs such as NOD1, NOD2, NLRP10, NLRX1, NLRC5, and CIITA do not directly engage the inflammatory caspases, but instead activate nuclear factor-kB (NF-kB), mitogen-activated protein kinases (MAPKs), and interferon (IFN) regulatory factors (IRFs) to stimulate innate immunity [32].

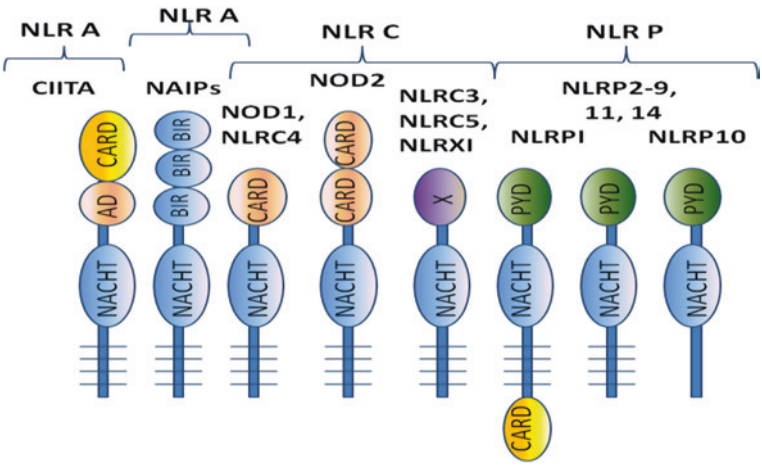

Fig. 8.4 Nod-like receptors

NOD-like receptors have been described as master regulators of innate immunity. NLRs are essential in recognition of microbial- and pathogen-associated molecular patterns (MAMPs and PAMPs), and have the ability to initiate and support robust immune responses through the formation of inflammasomes and the activation of NF-kB, IRF, and MAPK pathways. Functions such as the enhancement of MHC transcription and presentation implicate NLRs in adaptive immunity, and their roles in reproduction indicate a broader responsibility of this gene family than previously suspected. The potency of NLRs in inducing immune defenses is vital for the host, but can also provide serious problems when dysregulation or malfunction occurs (Fig. 8.4).

8.6 Heat Shock Protein/Chaperones

The concept of "protein interaction" is generally used to describe the physical contact between proteins and their interacting partners. However, protein interactions do not always have to be physical [33]. Protein interaction networks are useful resources in the abstraction of basic science knowledge and in the development of biomedical applications. Therefore, protein interaction networks can elucidate the molecular basis of disease, which in turn can inform methods for prevention, diagnosis, and treatment [34].

Microorganisms frequently change the pH of their own habitat by producing acidic or basic metabolic waste products. If the external pH decreases to 4.5 or lower, chaperones such as acid shock proteins and heat shock proteins are synthesized. Chaperones were first discovered because they dramatically increased in concentration when cells were exposed to high temperatures, metabolic poisons,

and other stressful conditions. Thus many chaperones are often called heat shock proteins or stress proteins. Heat shock proteins influence infectious disease processes in a number of diverse ways: they are involved in the propagation of prions, replication and morphogenesis of viruses, and resistance of parasites to chemotherapy. Several heat shock proteins function as intracellular chaperones for other proteins. They play an important role in protein-protein interactions such as folding and assisting in establishment of proper protein conformation (shape) and prevention of unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in transporting proteins across membranes within the cell [35]. These proteins also appear to be important mediators of bacteria-host interactions and inflammation, the latter via interactions with cell surface molecules and structures such as Toll-like receptors and lipid rafts. Heat shock proteins can be expressed on the surface of infected cells, and this is likely to provide a target for the innate immune response. Elevated levels of circulating HSP are present in infectious diseases and these proteins might therefore regulate inflammatory responses to pathogenic challenge on a systemic basis [36]. For many years it was believed that polypeptides would spontaneously fold into their final native shape, either as they were synthesized by ribosomes or shortly after completion of protein synthesis. Although the amino acid sequence of a polypeptide does determine its final conformation, it is now clear that special helper proteins aid the newly formed or nascent polypeptide in folding to its proper shape [37]. These proteins, called molecular chaperones, recognize only unfolded polypeptides or partly denatured proteins and do not bind to normal, functional proteins. Their role is essential because the cytoplasmic matrix is filled with nascent polypeptide chains and proteins. Under such conditions it is quite likely that new polypeptide chains often will fold improperly and aggregate to form nonfunctional complexes. Molecular chaperones are key players of the homeostasis of the proteome network and suppress incorrect folding and may reverse any incorrect folding that has already taken place [38]. Therefore, their expression and the activity are tightly regulated at both the transcriptional and posttranslational level at various age-related diseases (e.g., degenerative diseases and cancer) [39].

Chaperones and ATP-dependent proteases collectively engaged in the first line of defense of mitochondrial protein quality control (mtPQC) system, and this way it monitors the removal of oxidatively damaged polypeptides. For example, ‘Lon protease’ governs the removal of oxidized proteins in yeast and mammalian mitochondria [40].

8.7 Transmembrane Protein and Cellular Junctions

Many transmembrane proteins are also involved in the protection from infectious diseases. For example, interferon-induced transmembrane protein-3 (IFITM3) is a virus restriction factor mediating cellular resistance to influenza viruses and other viruses that enter cells via the acidic endosome [41]. Transmembrane mucins

and their *O*-glycans on the glycocalyx provide the transcellular barrier, a second layer of protection. Cell surface glycans bind carbohydrate-binding proteins that respond to extrinsic signals and modulates pathogenic responses. Apart from maintaining the homeostasis, it also restricts drug targeting of epithelial cells [42]. Some of the members of gap junction (GJ) family proteins like intercellular channels, which connect the cytoplasm of neighboring cells and hemichannels that connect the intra- and extracellular milieu, are also known to participate in physiologic and pathologic processes including electrical conduction, inflammation, immune system activation, tissue repair/remodeling, and response to bacterial and viral infections. However, little is known about the role of GJ channels in parasite infection.

8.8 Protection from Infectious Diseases

A number of proteins take part in protection of human body from external harmful agents. Keratin protein is a component of skin which is considered the first line of defense. This innate immunity component serves to prevent microorganisms from entering the body. Lysozyme, an enzyme present in tears and saliva, and thus, another protein also confer protection to the body. Likewise, almost all the elements of our immune system, e.g., Immunoglobulins (antibodies), various cell surface proteins (T and B cell receptors, Major histocompatibility complex, CD4, CD8, CD3, etc.), the several adaptor proteins and enzymes, involved in signal transduction pathways, are all of protein origin and crucial for combating against external infections.

Since peptides play a crucial role in the fundamental physiological and biochemical functions of life, they have for decades now attracted much attention for their potential therapeutic use. Compared with small chemical entity drugs, peptide-based drugs possess certain favorable characteristics, including:

- Higher potency: Peptide-based drugs generally are very active on their target receptor, which translates into a high effect at a low dose;
- Higher selectivity: Peptides can very tightly fit to their receptors, which make them much more selective than smaller molecules. This means that peptides tend to bind only to their target receptor and therefore are less likely to be associated with serious adverse side effects;
- Naturally occurring biologics—better safety: Peptides are naturally degraded in the blood stream by circulating enzymes to their component amino acids. As these are natural biological products, peptide drugs are also associated with less accumulation in body tissue and fewer toxicity findings also owing to their low doses.

There are a few challenges associated with the use of peptides like they are generally short-lived, cannot be administered orally and have low product stability.

Various peptide/glycopeptides drugs are administered: Vancomycin, Vasopressin, Insulin (recombinant), Nesiritide, Ceruletide, Bentiromide, Exenatide, etc.

Vaccination, composed of several natural and artificial proteins, is a key strategy for the control of various infectious diseases. Many pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis* produce on their surfaces dense and complex glycan structures, which represent an optimal target for eliciting carbohydrate specific antibodies able to confer protection against those bacteria. The traditional mechanism of action of glycoconjugates has considered peptides generated from the carrier protein to be responsible for T cell help recruitment. Progress of synthetic and biosynthetic methods for the preparation of glycoconjugates gives new insights for the design of improved carbohydrate-peptide conjugate vaccines [43]. Similarly, *Staphylococcus aureus* is a prominent cause of human infections worldwide and is notorious for its ability to acquire resistance to antibiotics. Methicillin-resistant *S. aureus* (MRSA), in particular, is endemic in hospitals and is the most frequent cause of community-associated bacterial infections in the United States. *S. aureus* produces numerous molecules that can potentially promote immune evasion, including protein A (SpA), an immunoglobulin (Ig)-binding protein present on the bacterial surface and freely secreted into the extracellular environment. This finding provides the foundation to develop a vaccine that prevents severe *S. aureus* infections [44].

8.9 Prion

Stanley B. Prusiner coined the term prion in 1982. It is basically derived from the words protein and infectious [45]. The protein that prions are made of (PrP) is found throughout the body, even in healthy people and animals. However, PrP found in infectious material has a different structure and is resistant to proteases, the enzymes in the body that can normally break down proteins. The normal form of the protein is called PrP^{C}, while the infectious form is called PrP^{Sc}—the *C* refers to 'cellular' or 'common' PrP, while the *Sc* refers to 'scrapie', the prototypic prion disease, occurring in sheep [46]. A prion in the Scrapie form (PrP^{Sc}) is an infectious agent composed of protein in a misfolded form [47]. So, they are not considered living organisms but may propagate by transmitting a misfolded protein state. If a prion enters a healthy organism, it induces existing, properly folded proteins to convert into the disease-associated, prion form; the prion acts as a template to guide the misfolding of more proteins into prion form. These newly formed prions can then go on to convert more proteins themselves; this triggers a chain reaction that produces large amounts of the prion form [48]. This altered structure is extremely stable and accumulates in infected tissue, causing tissue damage and cell death [49]. All long-term hematopoietic stem cells express PrP on their cell membrane and those hematopoietic tissues with PrP-null stem cells exhibit increased sensitivity to cell depletion [50].

A naturally occurring disinfectant exists within common lichens and might actually be able to stop prions in the wild. Christopher Johnson and his team describe experiments with lichens, symbiotic collections of algae, fungus, and bacteria that casual observers might mistake for moss. Three common species of lichens, the team has found, exude an enzyme that breaks down the prion. They showed that these lichen extracts efficiently degrade disease-associated prion protein (PrPTSE), the probable etiological agent of the transmissible spongiform encephalopathies (TSEs), and suggest that some lichens could have potential to inactivate TSE infectivity on the landscape or be a source for agents to degrade prions [51].

8.10 Conclusion

Proteins are one of the most important biomolecules, involved in any biological process of all living beings, playing useful as well as harmful roles in their survival. It is necessary to investigate these proteins, and to develop new biomedical tools and technologies, which will play a key role in evasion of various diseases, thus, saving and improving quality of lives. Further research is ongoing and should be carried out to explore this area of utmost concern.

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