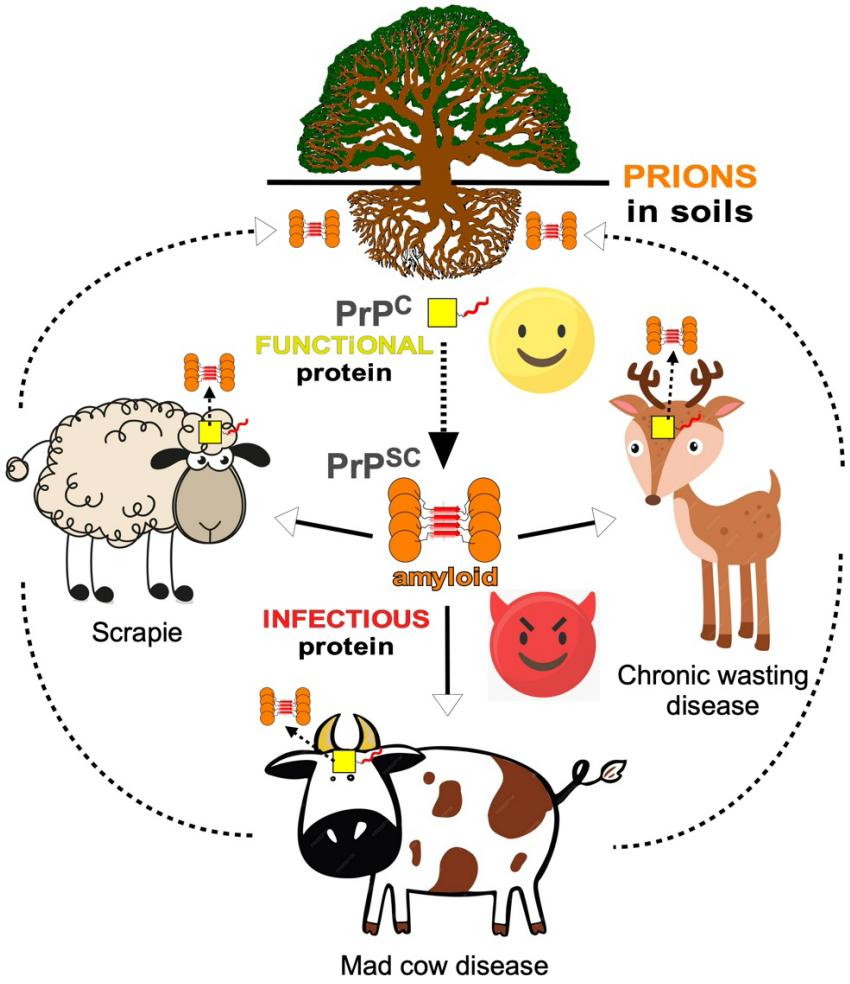
Prions: When proteins become infectious agents

Teacher to the class:
What is the smallest thing causing an infection?



The conversion of a functional protein (PrP^{C}, yellow squares) into an infective prion (PrP^{SC}, clustered orange circles) and its environmental cycle, including animals and soils. Credits: the author, using emojis and animal drawings from http://www.freepik.com

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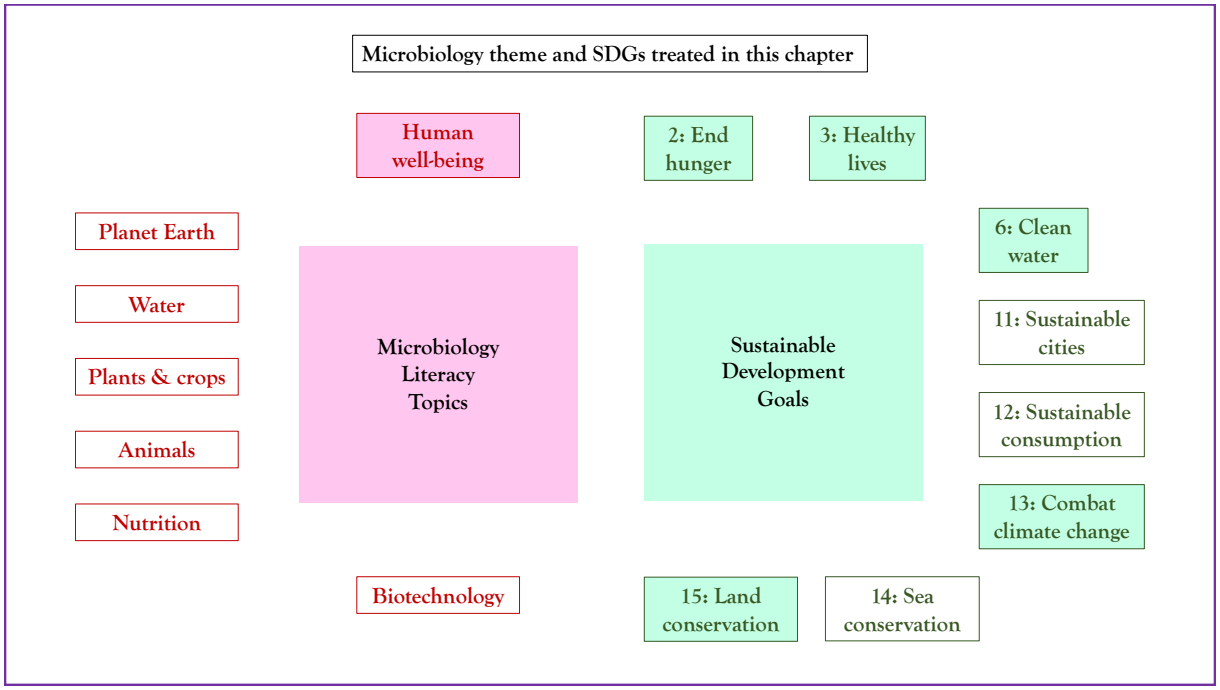
Prions

Storyline

We always link **infectious** diseases to microorganisms, either bacteria or fungi, and viruses too if we attribute the status of organism to these "messages in bottles", made of nucleic acid (either DNA or RNA) scripts inside a protein container. Thus, viruses are usually regarded as the simplest infectious agents… But not quite. Due to its sequence composition, to **mutations** or **amino-acid** modifications, a given protein can lose its normal form and become sticky, sticking to other members of the same protein to form tight aggregates of extreme strength that cells cannot get rid of. Such aggregates, termed **amyloids**, have the power to kill cells (and large organisms as well) and, once released, they can convert other molecules of their own kind that they may encounter just by touching. These proteins thus become infectious particles (*aka* **prions**), much smaller than any virus and with no constituent DNA or RNA. However, not all prions are **pathogenic**, but can also have cellular functions. Thus, as for microorganisms themselves, nothing in biology is 100% "good" or "bad".

The Microbiology and Societal context

The microbiology: proteins as infectious agents; yeast prions; bacterial amyloids in biofilm matrices and prions in gene regulation. *Societal issues*: animal prion diseases and their impact on farming and wildlife; prions as persistent soil contaminants; threats of prions for human health under a One Health perspective; bacterial amyloids in neurodegenerative diseases? *Sustainability issues*: zero hunger (2); good health and wellbeing (3); clean water and sanitation (6); climate action (13); life on land (15).



Prions: the Microbiology

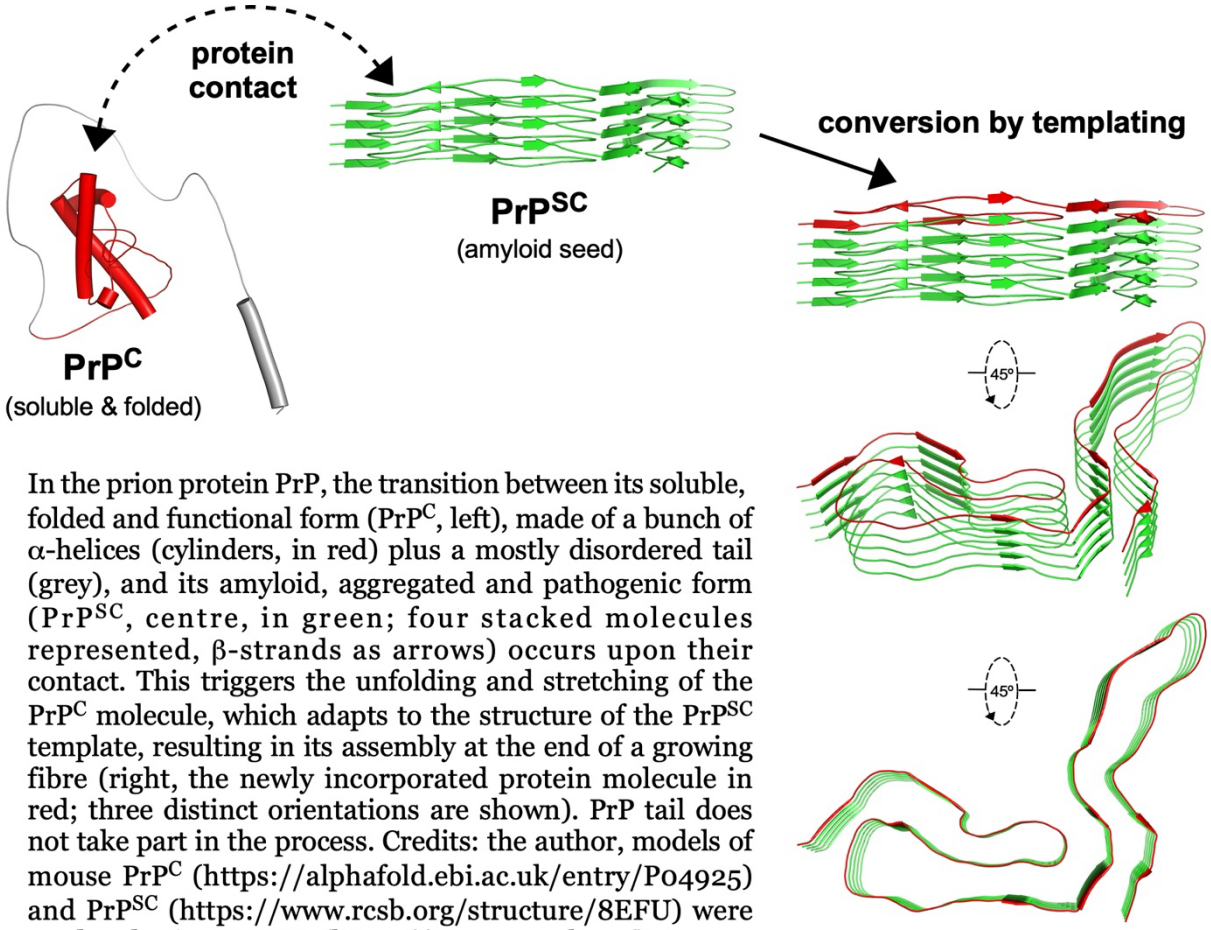
1. Information flow in the cell: decoding and functional implementation of the genetic code. The "central **dogma**" of molecular biology states that DNA is the core information-rich molecule, templating intermediate instruction sheets (messenger RNA) that are read and converted by **ribosomes** into proteins. Proteins are the final battle horse molecules in any cell (microorganisms included) by scaffolding cellular architecture and carrying out most of its regulatory and catalytic functions. Although proteins have intricate three-dimensional structures (now accessible to all, thanks to novel AI tools), they were considered to be the information-depleted, dead-end products of genetics. Not anymore: as initially discovered in yeast and bacteria, and then extended to all organisms, protein aggregates like prions can be efficient (and beneficial) switches between two alternative functions for a given protein, as a quick response to changing environmental conditions.

2. Prions are proteins with the potential to cause infectious diseases. Everybody knows that infections can be caused by bacteria, viruses and even by fungi, although on the other hand microorganisms mostly have beneficial actions on our planet. This is true in most cases, but there is a kind of protein (that is, complex hank chains made of linked amino-acids) called prions that can act as infectious agents. Prion proteins have a natural, spontaneously acquired fold in which they are functional (e.g., as regulators of genes or as signalling receptors). However, as a response to environmental challenges (such as temperature increase or acid media) to their binding to other molecules (DNA, RNA, complex sugars), or to mutation-favoured changes in their **3D structure** (*aka* **conformation**), prion proteins aggregate as layered and recalcitrant assemblies, much like Lego constructions, termed amyloids. The minimal size of a prion aggregate showing infectivity can be around 10 nanometres (1 nm is the millionth part of a millimetre), about ten-fold smaller than the average virus.

3. Prion templating. An amazing (but frightening) thing is that prions can attract to themselves more molecules of the normal (native state) protein and convert them into prions through contact (biochemical interaction), which sounds a bit like what vampires can do, which immediately assemble into amyloids. Furthermore, minute differences in the structures of the amyloid templates (often called "seeds") lead to the propagation of prion **strains** generating distinct **phenotypes** (e.g., disease symptoms). As a result, if an animal (or indeed, one of us) accidentally eats food contaminated with prions from infected animals (e.g., grass in pastures contaminated with faeces or the remains of dead animals), it can also become infected.

In fact, this happened long ago to the members of the Fore tribe living in the highlands of New Guinea who ate the tissues, including the brains, of deceased family members (ritualistic cannibalistic consumption). As a result, the tribe suffered seriously from the brain disease *Kuru* which was only erradicated when the practice of ritualistic cannibalism was discouraged. However, this strange disease prompted new research which led to the discovery of the unique prion affecting humans, PrP. So, prions might be described as "zombie proteins"!

PrP is a protein present in the brain of all mammals, which in the 1980's was found to convert from its functional form (PrP^{C}) into infective amyloid aggregates (PrP^{SC}). PrP^{SC}, after a long-term incubation, generates a **neurodegenerative** disease in humans, the *Creutzfeldt-Jakob disease* (CJD). CJD, as well as other related diseases caused by distinct PrP^{SC} strains, are all fatal, i.e., they are lethal and there is no cure for them, neither a **vaccine** nor a **drug**.



In the prion protein PrP, the transition between its soluble, folded and functional form (PrP^C, left), made of a bunch of α-helices (cylinders, in red) plus a mostly disordered tail (grey), and its amyloid, aggregated and pathogenic form (PrP^{SC}, centre, in green; four stacked molecules represented, β-strands as arrows) occurs upon their contact. This triggers the unfolding and stretching of the PrP^C molecule, which adapts to the structure of the PrP^{SC} template, resulting in its assembly at the end of a growing fibre (right, the newly incorporated protein molecule in red; three distinct orientations are shown). PrP tail does not take part in the process. Credits: the author, models of mouse PrP^C (https://alphafold.ebi.ac.uk/entry/P04925) and PrP^{SC} (https://www.rcsb.org/structure/8EFU) were rendered using PyMOL (https://www.pymol.org/)

4. Yeast prions. By the middle 1990's it became clear that **budding** yeasts, the wonderful microbial fungi behind the **fermentations** that produce bread, wine and beer, used the aggregation into amyloids of some of their proteins as a mechanism to switch genetic **circuits** off in response to rapid environmental changes. In order to stick to each other as amyloids, such yeast proteins used flexible tails made of repeated sequences with simple amino-acid compositions. Through the formation of amyloids by some particular proteins, yeasts expanded the whole protein repertoire (the **proteome**) by ignoring the stop instruction that ends mRNA **translation** (due to Sup35 aggregation), or by shifting the source of nitrogen-containing nutrients (Ure2 aggregation).

Because such amyloid aggregates were inherited by daughter cells from the dividing mother cell through the budded **cytoplasm**, or through cytoplasm fusion during cell **mating** (the kind of rudimentary sexual reproduction that occurs in yeast), the involved proteins were considered as prions (termed [*PSI*$^+$] for Sup35, and [*URE3*] for Ure2, in the examples above). Nowadays, hundreds of prion proteins have been identified in yeast, regulating many "vertically inheritable" characters. It is still under debate if prions are also detrimental to yeast, either due to the burden linked to amyloids or to the collateral effect of the loss of the original protein function.

5. Bacterial prions. When bacteria need to persist in the environment, they often attach to surfaces, forming clumps or sheets of cells called **biofilms**. These are very important for enhancing the resistance of bacteria against antimicrobial treatments and other environmental challenges.

Since the early 2000's, it is known that essential components glueing bacteria together in biofilms are in fact amyloid fibres formed by **extracellular** proteins (the most studied ones are CsgA, FapC, Bap and PSMs) produced by the component bacteria. Although these proteins share the amyloid structure with prions, they are not prions themselves, because they do not propagate to other bacteria in an infectious manner. However, as we shall see later on, they still might have a role in the onset of some human diseases.

Are there prions in bacteria? The answer is yes! RepA, a protein that triggers DNA **replication** of a **plasmid** in *Pseudomonas*, was found to have a region called the WH1 **domain**. This domain is not like prions in yeasts with unstructured tails, but is initially compactly folded and with the ability to form amyloid fibres. RepA-WH1 propagates as a prion in bacteria from mother to daughter cells, presenting itself as two distinct forms. What is fascinating: it causes a sort of "disease" in bacteria, by causing newly-synthesized RepA-WH1 molecules to form amyloid which finally stops cells from dividing and to die. In this sense, RepA-WH1 is like the PrP prion, thus constituting a very simple and safe (i.e. it cannot infect humans) **model** for a prion disease.

Computer surveys of flexible yeast-like prion sequences subsequently revealed that they exist in hundreds of bacterial species. However, thus far in only two instances, the *Clostridium* Rho terminator of mRNA **transcription** and a *Campylobacter* protein that packages single-stranded DNA, have experiments demonstrated that, besides aggregating as amyloids, they can be vertically inherited during cell division and result in a change in bacterial biology.

6. Animal prions and their impact on farming and wildlife. In animals, prion-caused diseases include *scrapie* in sheep and goats, *mad cow disease* in cattle and *chronic wasting disease* (CWD) in cervids (hoofed ruminants, like deer). Fortunately, the incidence of these diseases is (as yet) low. In addition, the frequency of **cross-species** infection is also very low due to the existence of "species barriers" determined by natural variations in the sequences of their PrPs.

Scrapie was known to affect herds of sheep as early as the XVIII century, although its attribution to a prion disease is recent. In the case of the *mad cow disease*, the only prion disease in which **zoonotic** oral transmission has been demonstrated from animals to humans, infection is efficiently prevented through the sanitary control of the food chain, bovine meat in our case and fodder for cattle. However, the emergent CWD is affecting with increasing prevalence both wild and domesticated populations of all deer species native to Canada and USA in America, Scandinavian countries in Europe and South Korea in Asia. The socioeconomic impact is large since hunting is a traditional core activity in indigenous communities, significantly contributing to their protein intake. Furthermore, the impact of a potential disappearance of major herbivores in forest **ecosystem**s would be disastrous.

7. Prions are persistent environmental contaminants. Prion aggregates are very resistant to degradation by the enzymes (called **proteases**) that nature uses to eliminate proteins when they become old or damaged, by chopping them back to their amino-acid building blocks, which are then recycled to form new proteins. Furthermore, prions stick to and are protected by organic and mineral components of soils, plant leaves and shoots, and can survive transit through the gut of **arthropods** and earthworms. This endows upon prions long term persistence, to the extent that fields infected with scrapie prions can remain contaminated for many decades.

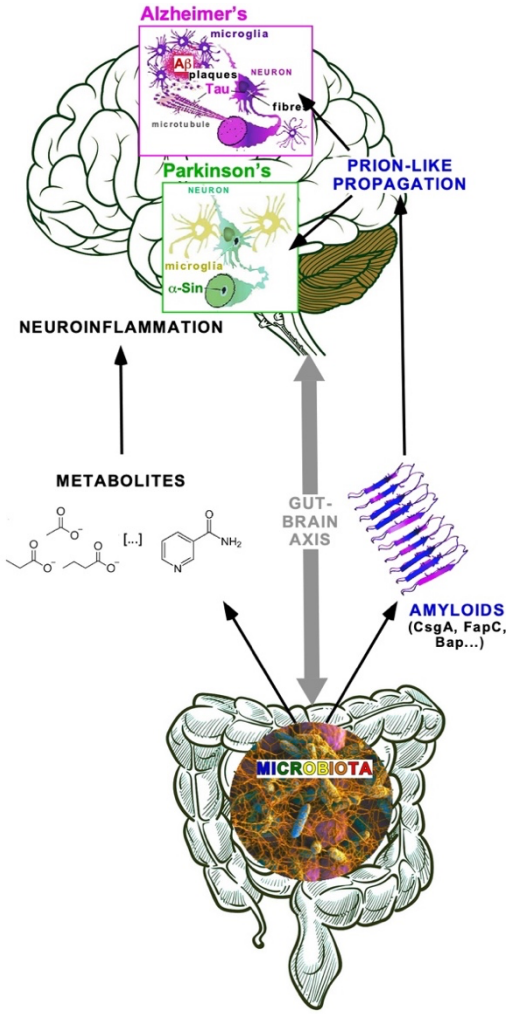
Solutions currently available to remove prions from infected soils are not sustainable: either to fence and abandon the affected fields, or to mechanically remove precious fertile soil for destruction, and to kill infected and potentially infected animals and incinerate their bodies, with the associated consumption of fossil fuels and CO_2 release. A **bioremediation** solution for prions is still lacking and eagerly awaited.

8. The One Health perspective: threats of prions for humans. Late in the 1980's and 1990's a worldwide health alarm was triggered when, in the UK and later on in other countries in the EU, an increase of a variant of CJD affecting humans who had eaten meat products from cattle infected by PrP^{SC} was observed. The so-called *mad cow disease* happened because those animals had been fed with fodder that included, as a protein supplement, parts of the bodies from cows that had (spontaneously) developed the disease. This terrible CJD variant was eradicated simply by the strict banning of the inclusion of meat derivatives in the food chain of cattle.

However, freely foraging sheep and deer are increasingly affected by *scrapie* and CWD, which also are matters of concern from a **One Health** perspective. Fortunately, though, these prion diseases have not so far been reported to be passed on to humans. Thus, they are currently submitted to veterinary vigilance, and meat from the affected animals, as in the case of the *mad cow disease*, are kept out of the human food chain.

9. Bacterial amyloids in neurodegenerative diseases? Based on the two aspects outlined above, that prions can cause neurodegenerative diseases and that prions are found in many bacteria, a simple question arises: might bacterial prions in our **microbiota** be a threat for human health? There is much ongoing research on human proteins involved in other neurodegenerative diseases (such Tau and the ß-amyloid peptides in Alzheimer's, or α-synuclein in Parkinson's), which are under consideration for being (or not) prions. It is known that upon the aggregation of such proteins as amyloids, they cause the death of neurons in the brain. Such aggregates released from the dying cells can be captured by neighbouring cells in which they induce the same proteins to aggregate as amyloids, thus slowly propagating the disease across distinct areas in the brain. Because this ability to be locally infectious in tissues, the Tau or α-synuclein aggregates are considered "prion-like", although conclusive evidence for their *natural* infectivity (because experimentally-induced infections can be caused) between distinct individuals is still lacking.

Recent findings point to the ability of bacteria in the gut microbiota to influence the behaviour of their hosts, either animals (e.g., mice, worms and flies) or humans. They appear to do so through the secretion of molecules (**metabolites**) that, once absorbed through the gut into the blood, induce **inflammation** in some areas of the brain. What is relevant to our story is that it has been also found that the extracellular amyloids that we have already mentioned (in particular CsgA and Bap), when generated by some bacterial species that are predominant under non-healthy conditions (**dysbiosis**), can eventually find their way to the nervous system in animals with a fragile gut epithelium. This internal "highway" is a fascinating connection termed *the gut-brain axis*. There is quite intriguing evidence on bacterial amyloids that, once they have reached the brain, they can template on a human protein (in particular α-synuclein or Tau) its aggregation as amyloids, thus triggering the onset of neurodegeneration (Parkinson's and Alzheimer's diseases, respectively). The confirmation of these findings and their impact on new therapies are now subjects of very active research.



The possible participation of some microbes in the gut, through their metabolites and amyloids, in the onset of neurodegenerative diseases. Credits: the author, modified from https://analesranf.com/articulo/9001_04/.

Relevance for Sustainable Development Goals and Grand Challenges

- **Goal 2. End hunger and achieve food security**. Animal farming is a continuous, central activity for providing food to humans since the Neolithic times (about 9,000 years ago). The zoonotic potential of the infectious prion disease caused by PrP^{SC} is a matter of concern for food security, besides causing huge economic losses, in farming sheep, goats and cows and, on a more local scale, also deer and, more recently, even camels. For some communities, such as Eskimos and Lapps, the food provided by domesticated reindeer and caribous is a major protein source in their diet, in addition to the place of these animals at the core of their cultures. In addition, deer hunting is a traditional activity and also a major source of protein intake for rural communities in Canada and the northern states in USA.
- **Goal 3. Good health and wellbeing**. Related to SG2, with origin in the meat of mammals, prion diseases impose strict safety controls on a large portion of our usual protein sources. Such controls are not easily accessible to the primary producers (farmers), because they imply the existence and proximity of both technological resources and a trained network of scientists to provide quick and efficient detection of prions in the affected animals before they enter into the food chain. Even more, they are out of reach of rural

communities in developing countries. These factors must be additional boosters to scientific research on prions, including inhibitors of prion propagation, and to the current efforts to find complementary/alternative **sustainable** protein sources. Much research is still required to study the potential of bacterial amyloids and prions, especially in scenarios of gut microbiota dysbiosis, in the onset of human neurodegenerative diseases. This would include the development of probiotic formulations and faecal transfers as ways to recover a healthy balance of the microbiota.

- **Goal 6. Clean water and sanitation**. Although prions are retained in soils and on the surface of plants, there is also the possibility for their partial removal by rain or irrigation water, with subsequent transport (albeit very diluted) to natural water springs and ponds, in which they might then be available to infect animals or humans upon drinking or plant consumption. There is no consistent evidence on the capacity of the **protocols** applied in conventional wastewater treatment plants, or of water **chlorination**, to inactivate prions, although results from small scale studies with diverse chemicals on distinct surfaces are promising.
- **Goal 13. Climate action**. Beyond the contribution of cattle to global carbon emissions, current protocols for disposal of the bodies of prion-infected animals after culling, and for treatment of contaminated soils, by burning in furnaces liberates to the atmosphere unacceptable amounts of CO_2 from the organic matter, as well as the fossil fuels used to operate the furnaces. In the quest for safer and more sustainable farming practices, achieving bioremediation of prions must be a priority.
- **Goal 15. Life on land**. The CWD is a major menace for all deer species in the world that could eventually be driven to extinction in forest areas in which they precisely occupy the cusp of the primary consumers (herbivores). This will have vast implications for the maintenance of balanced trophic (food) chains in forests across the northern hemisphere, by imposing constraints to the population sizes of their predators (i.e., the large carnivores such as bears, wolves, pumas, etc.)

The Evidence Base, Further Reading and Teaching Aids

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Glossary

3D structure: the disposition of all atoms in a complex molecule, either biological or not, across the three dimensions of space, usually as a computer-generated graphic representation.

AI: Artificial Intelligence. The most advanced software approaches based on the ability of neural-inspired networks to learn. Invaluable for the comprehensive integration of complex data on biological systems.

amino-acid: each one of the 20 building blocks of proteins. They are linked, through amide (N-CO) chemical bonds, in a precise sequence by the ribosome during 'translation' of mRNA, the process of reading the genetic message instructions.

amyloid: assembly of protein molecules through beta-strands (schematically represented as arrows), thus piling-up to build fibres. These are among the most stable biological structures and can either confer advantageous properties or be harmful to cells promoting diseases (amyloidosis). Prions are made of amyloid.

arthropod: the most populated *Phylum* of animals on Earth, includes (among others) insects, crustaceans and arachnids. They are major actors in zoonoses, able to bear and transmit bacterial, fungal and viral diseases, but not prions so far.

biofilm: consortium of bacterial (and other microbial) cells that attach together forming a persistent matrix on natural or artificial surfaces. Biofilms are resistance forms adopted by bacteria against a number of stresses and threats, including drying, thermal stress of antibiotic treatment.

bioremediation: the action of metabolic removal and processing of environmental pollutants, usually by the use of natural or engineered microorganisms which modify or degrade them through their biochemical activities.

budding: a common way of mitotic cell division in some yeast, such as the baker's yeast, in which a large (mother) cell segregates and releases a smaller vesicle (buds) from its surface, including a full copy of its genome together with a set of the essential cellular machinery components. The bud thus becomes an independent (daughter) cell.

chlorination: the action of disinfecting/sanitizating (i.e., reducing the microbial load) of water supplies, or any other media, with chlorine-containing chemical compounds. Usually, it does not result in complete sterilization (neither with prions) and poses an environmental problem because its broad, unspecific toxicity.

circuit: in genetics, the network of genes and their regulatory proteins/RNAs that integrate to get a controlled (e.g., signal-responsive) expression of phenotypes (enzymatic reactions, colour, development, etc.)

conformation: a particular three-dimensional arrangement (fold) of the amino-acid residues in a given protein (or nucleotides in DNA/RNA). It is now a common finding that proteins can adopt more than one conformation, potentially each having a different function.

cross-species: the ability of some pathogens to infect/propagate in distinct hosts. In the case of prions, they can be transmitted between some evolutionarily close species (in terms of divergence of their PrP sequences), while there are barriers that make difficult their propagation to more distant ones.

cytoplasm: bounded by the cell membrane, the liquid/gel component of any cell interior including salts, metabolites, enzymes, scaffolding proteins, RNAs… In eukaryotic cells (e.g., yeast),

DNA is segregated from the cytoplasm within a membrane-wrapped nucleus, while in prokaryotes (bacteria and archaea) DNA is compacted at the cytoplasm in a territory called the nucleoid.

dogma: any knowledge sustained on authoritative grounds (i.e., masterful statements). In Science, sustained proof over time (especially by respected master scientists) for a hypothesis may derive in a sort of consolidated common wisdom. In molecular biology, "central dogma" is usually referred to "DNA makes RNA, makes protein", as stated by F.H.C. Crick in 1957, but exceptions have been found over time, including reverse transcription (RNA → DNA) and prions as proteins templating information.

domain: any part of a protein sequence able to self-organize as an independent, stable folding unit, often linked to a distinct, defined function (e.g., catalysis, adhesion, etc.). This concept sometimes is relaxed to be confounded with "motif", a distinguishable sequence pattern within a domain, or with a functional intrinsically disordered region.

drug: a chemical or biological (e.g., an antibody) compound with measurable inhibitory effect on a particular target (usually a protein). Drugs are the core of pharmacology in therapy and invaluable tools in research.

dysbiosis: an alteration in the microbiota affecting its species composition and diversity. It can be either the consequence or the cause of a disease and it is sensitive to diet.

ecosystem: the integrated whole set of organisms (from microbes to plants and animals, including us) and the physical environment (soil, water, atmosphere), with their mutual relations, that share in equilibrium an area, from the local to the large scales (e.g., regional or even continental).

extracellular: anything located outside cells, either in the space between them (culture media, tissular space, plasma, etc.) or attached to the cell surface and displayed outwards.

fermentation: an enzymatic process carried out by microorganisms that is core to their energetic metabolism in the absence of oxygen (anaerobic conditions). Fermentation has a central role in food processing, e.g., the transformation of sugar into CO_2, H_20 and ethanol by yeast in the production of bread, beer and wine, or lactose in milk into lactic acid by bacteria in the production of yoghurt.

infectious: in some microorganisms (either bacteria, fungi or viruses) the property of being transmitted from one host (cell or organism) to other. For prions, infectivity is also termed "horizontal" transmissivity.

inflammation: the immunological response of cells and tissues to infection, caused by recognition of some structural components of the microorganisms (e.g., the lipopolysaccharide of Gram-negatives' cell wall). Although crucial to overcome infection, because it involves an amplification cascade of host cell factors, inflammation can damage the infected host if it is excessive or becomes uncontrolled as in septic shock.

mating: it is the kind of sexual reproduction in yeast, which present two possible sexes (a and α). Two distinct a and α haploid (1 set of chromosomes each) cells chemically attract each other and fuse (mate) joining and mixing their genomes, thus getting a diploid cell (2 complete sets of chromosomes).

metabolites: the myriad of distinct chemical compounds in cells which are intermediate steps or final products of biochemical reactions, either of synthesis or degradation. They can be generated in one group of reactions to be used by another, or even act as signals between cells. Together with catalysts (enzymes) and energy-rich molecules (such as ATP), metabolites build all biochemical pathways.

microbiota: a consortium of microorganisms of different kinds (phyla, genera, species) sharing the same location (either in the environment or as commensals of plants and animals) and relating to each other through mutually beneficial or competitive interactions.

model: any simplified approach to the knowledge of a complex system, either through computational (mathematic algorithms or expressions) or imaging (representation of molecules, either realistic or schematic) tools. By extension, a simple (micro)organism studied to address as a short cut the biology of more complex ones.

mutation: a change in the genetic material (DNA) that it is inherited by the next generation(s). Can result from a single residue (nucleotide) change, elimination (deletion) or insertion to larger changes (usually of the two latter types) affecting whole genes, their regulatory sequences or even extensive chromosome regions.

neurodegenerative: a disease affecting the nervous system, either neurones and/or their supportive glial cells. They usually show a slow progression, thus manifesting themselves in old age, and have no cure, many being fatal.

One Health: a comprehensive approach to the study, prevention and therapy of infectious diseases that takes into account the integration of (and the interactions between) animals, humans (including our activities) and the natural environment.

pathogenic: said of a microorganism that causes disease.

phenotype: any measurable manifestation (usually in the aspect or function, at any level from molecules to whole organism) of genes (genotype), including its modulation by the environment.

plasmid: a molecule of circular DNA with autonomously regulated replication. Very common in bacteria (and yeast), plasmids carry genes that are valuable for adaptation of their host microorganisms to distinct environmental conditions and can be transferred horizontally between bacteria.

prion: a protein that acquires an aggregated amyloid conformation, which is self-replicative/templating and can propagate both vertically (mother-to-daughter upon cell division) and horizontally (infection of neighbouring cells).

proteases: a specialized type of enzymes whose catalytic activity is to cleave peptide chemical bonds, thus degrading proteins into their component amino-acids. They are crucial both for retrieving nutrients from protein sources in foods and for quality control and elimination of damaged proteins in cells.

proteome: the whole content of the proteins in a cell. Can refer to a particular subset expressed under a defined condition (e.g., thermal, acid or starvation stresses) and may vary over time.

protocols: detailed formal instructions on how to carry on procedures either at a laboratory or industry, or in many other human activities.

replication: the copying of the genetic material by dedicated proteins, some of which (polymerases) use each of the two strands of DNA as a mould (template) to synthesize the other by successively linking together the complementary nucleotide bricks.

ribosome: complex nanomachine, made of RNA and proteins, that synthesizes proteins in cells.

strain: a lineage in any microorganism that carries a particular genotype variant (i.e., differs from a close relative by mutation), often with an associated phenotype. For prions, this concept applies to any distinct conformation of a prion protein in its aggregated amyloid form, usually also reflected as a particular phenotype.

sustainable: a process or manufacture having the quality of being made of, and maintained through, renewable materials and energy sources.

templating: the capacity of some complex biological molecules to mould on themselves their synthesis (as for nucleic acids) or their three-dimensional structures (as in prion proteins).

transcription: the biological process by which the information stored in DNA is passed to RNA by the action of specialized enzymes (RNA polymerases) that copy genes into ribonucleotide chains on a DNA strand template. A number of regulatory protein (and RNA) factors coordinate transcription as demanded by cell function.

translation: by the ribosomes reading the genetic message (mRNA) through its complementary pairing with RNA molecules (tRNA) charged with precise amino-acids. These are joined together, in the order imposed by mRNA sequence, by the catalytic action of ribosomal RNA.

vaccine: a prophylactic (preventive) medicament delivered to humans (and animals) to train their immune systems against the possible infection by a pathogen. Can be administrated by different ways (injection, orally, etc.) and consist of live attenuated (non- or only weakly pathogenic variants) organisms (e.g. live polio vaccine), whole inactivated (killed) microorganisms (whole cell vaccines) , or their components, such as proteins (subunit vaccines) or, more recently, mRNAs.

zoonotic: said of an infectious disease that, having its origin (and natural transmission) in animals, subsequently gains the ability to infect humans. Many of our current infectious diseases (such as flu or COVID-19) have a zoonotic origin, which is a major concern from a One Health perspective.