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Almost a century of prion protein(s): From pathology to physiology, and back to pathology

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ABSTRACT

Prions are one of the few pathogens whose name is renowned at all population levels, after the dramatic years pervaded by the fear of eating prion-infected food. If now this, somehow irrational, scare of bovine meat inexorably transmitting devastating brain disorders is largely subdued, several prion-related issues are still unsolved, precluding the design of therapeutic approaches that could slow, if not halt, prion diseases.

One unsolved issue is, for example, the role of the prion protein (PrP^C), whole conformational misfolding originates the prion but whose physiologic *reason d'etre* in neurons, and in cells at large, remains enigmatic. Preceded by a historical outline, the present review will discuss the functional pleiotropicity ascribed to PrP^C, and whether this aspect could fall, at least in part, into a more concise framework. It will also be devoted to radically different perspectives for PrP^C, which have been recently brought to the attention of the scientific world with unexpected force. Finally, it will discuss the possible reasons allowing an evolutionary conserved and benign protein, as PrP^C is, to turn into a high affinity receptor for pathologic misfolded oligomers, and to transmit their toxic message into neurons.

Contents

1. Prions and prion diseases: a brief historical outlook

As it often happened, particularly at times when pathogens were largely mysterious, the first example of the human pathology we now know to be caused by prions, was not named after the pathologic agent but after two clinicians, Hans G. Creutzfeldt and Alfons M. Jacob, recognizing around 1920 atypical neurodegenerative forms leading rapidly and invariably to death with atrocious symptoms [1,2]. Sadly, this dramatic outcome, which characterizes late-onset Creutzfeld-Jacob disease (CJD) and similar pathologies (e.g., fatal familial insomnia) [3], but also the variant CJD caused by bovine prion-contaminated food [4], remains largely unchanged after a century, despite identification of the etiological agent during this period of time.

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This decade-long effort has witnessed the contribution of different scientific approaches: initially from veterinarians, biologists and physicists, highlighting that the agent of the sheep disease (called scrapie) was infectious [5] and unusually resistant to procedures inactivating viruses and bacteria [6]; then from other brilliant minds, e.g., the physician and anthropologist Daniel C. Gajdusek, suspecting and then proving the infectious basis for the endemic brain degeneration (named kuru) that ritual cannibalism was producing in distant Papua New Guinea [7,8]; or the mathematician John S. Griffith, theorizing an unorthodox origin for the scrapie agent [9]; finally biochemists, obstinately pursuing segregation of a brain infectious fraction, and calling it prion (PRoteinaceus Infective ONly particle) after establishing its protein nature [10]. The subsequent years were principally devoted to determine the biochemical and pathological aspects of the prion, culminating in the identification of a gene unexpectedly coding for both the prion major constituent, thereafter named "scrapie" prion protein (PrP^{Sc}), and a native cell component ("cellular" prion protein, PrP^{C}) [11].

Identical primary sequences and post-translational modifications of the two proteins [12] thus claimed that the central event in prion diseases had to be an aberrant conformation of PrP^{C}. Indeed, such a structural misfolding generates a β sheet-enriched conformer (PrP^{Sc}) with novel physico-chemical properties, which account for insolubility and proteolysis resistance of PrP^{Sc}-aggregates (amyloids), a common hallmark of diseased brains, and for insensitivity to classical pathogen-inactivating procedures. The key feature of the PrP^{Sc} conformer is, however, the capacity to self-propagate in a host organism by acting as a template for the exponential misfolding of native PrP^{C} molecules [13]. That the PrP^{C}-PrP^{Sc} conversion is key to prion generation was eventually firmly established by the resistance of PrP-knock out (PrP-KO) animals to prions [14], and by generating "artificial" prions from recombinant PrP forms retaining replicative and infectious properties of the naturally-occurring ones [15].

Although prion diseases are by far less common than other neurodegenerative disorders (one case over 10^6 people per year), the astounding advancements in the prion field have generated the so called "prion principle", which is now generally adopted to explain the cell-to-cell spreading of self-replicating neurotoxic misfolded proteins and the existence of conformational strains. The reader is referred to other contributions to this section to appreciate all details, and applicability limits, of the afore-mentioned concept.

The demonstration that, instead of nucleic acids as in viruses and bacteria, self-replicating pathogens could be constituted by a protein has radically changed the concept of infectivity. Inevitably after the prion isolation, the necessity to fully define such a "new" agent has left aside the issue of PrP^{C} physiology that, although revitalized in recent years by the urge for diagnostic and therapeutic tools, remains elusive.

2. Physiology of PrP^{C}

PrP^{C} is a glycoprotein of around 230 aminoacid residues linked to the external cell membrane by a glycosylphosphatidylinositol (GPI) anchor. It is ubiquitously expressed in all mammalian species, particularly in neurons and in the lympho-reticular system [16]. As mentioned, PrP^{C} physiology is not yet solved, not even after availability of PrP-KO mice [17], also postnatally [18], given that these animals display no obvious developmental or behavioral defect (for a review see Ref. [19]). It is however possible that compensatory mechanisms could hide the PrP-KO phenotype under normal conditions, and that the absence of PrP^{C} manifests clearly only during stress conditions as was reported in brains exposed to ischemic, or inflammatory, injury [20–24]. Other studies have reported that absence of PrP^{C} could become evident with age, in light of mild cognitive deficits, nerve demyelination, muscle alterations and increased pain sensitivity recognized in aging PrP-KO mice [25–31]. Nonetheless, an impressive number of possible functions has been postulated, all of which beneficial to the cell life, ranging from protection against oxidative insults, to involvement in differentiation and signal transduction, to synaptic plasticity including learning and memory. As the current review will concentrate to selected hypothesized roles for PrP^{C}, we refer to a number of reviews for primary references and for an exhaustive coverage of the issue [32–34].

3. PrP^{C}, a defense against oxidative stress

Oxidative stress is one major cause of cell dysregulation and death. It arises when the cell redox equilibrium is altered and excessive production of reactive oxygen species (ROS) overcomes total antioxidant activities and provokes damages to all types of molecules. By affecting pumps and channels and mitochondrial respiratory components, a key consequence of oxidative stress is a dangerous Ca^{2+} load in different cell compartments, including mitochondria. This may lead to the opening of the mitochondrial transition pore that collapses the membrane potential, releases key matrix components and pro-apoptotic factors, and eventually triggers cell death [35]. Oxidative stress injuries have been recognized in multiple pathologies, ranging from cardiovascular and autoimmune diseases, to neurodegenerative disorders [36], including prion diseases [37].

ROS result from many reactions in different cell sites. One of these is the Cu^{2+}-based Fenton reaction, which takes place particularly in synaptic clefts where free Cu^{2+} concentrations could increase during physiologic neuronal depolarization [38]. Numerous studies thus aimed at relating the capacity of PrP^{C} to coordinate up to six Cu^{2+} (at N-terminal His residues with femto-to nano-molar affinity [39]) with a possible prevention of ROS damage at synaptic terminals where PrP^{C} preferentially localizes [40,41]. The observation that Cu^{2+}-PrP^{C} complexes have an accelerated endocytosis is also consistent with the ability of PrP^{C} to sequester toxic free Cu^{2+} and to remove the ion from the synaptic cleft [42].

The implication of PrP^{C} against oxidative stress was mainly assumed from comparing wild type and PrP-KO neuronal (primary or model) cells or mouse brains. These studies confirmed that PrP^{C} protected from oxidative injuries also by increasing the expression of antioxidant enzymes [43–51]. Other reports on brains subjected to focal ischemia generating significant ROS amounts have evidenced an increased expression of PrP^{C} [52,53], and that ischemic damages inversely correlated to PrP^{C} levels [52,54,55]. Interestingly, it has been demonstrated that PrP^{C} reduces ROS production also in intact hearts by modulating the expression (or activity) of ROS-removing catalase and ROS-generating $p66^{shc}$, and that it protects the myocardium from oxidative damage [56].

Examination of oxidative stress markers in brains derived from control and prion-infected mice further supported the contention that prion-induced loss of PrP^{C} functions (see below) impairs neuronal defenses against oxidative injury [57–61]. More recently, the focus shifted to the unfolded-protein response (UPR) that the endoplasmic reticulum (ER) activates to restore ER homeostasis in response to endogenous or exogenous insults, including accumulation of misfolded proteins (Fig. 1). The predominant UPR response promotes synthesis of ER proteins involved in folding or degradation processes [62], but also repression of mRNA translation by the pathway composed of the RNA-activated protein kinase R-like ER kinase (PERK) and the eukaryotic initiation factor 2α (eIF2α). During prolonged activation, UPR may, however, fatally compromise

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