Chapter 11
Transgenic Mouse Models in Prion Transmission Studies

Qingzhong Kong

Abstract Prion diseases are a unique group of mostly transmissible neurodegenerative diseases where the ubiquitous cellular prion protein (PrP^C) plays a central role. Numerous transgenic mouse models have been instrumental in dissecting the roles of PrP^C and other factors in the replication, pathogenesis, and transmission of the prion agents. This chapter summarizes the seminal roles of transgenic mouse models in prion transmission studies with an emphasis on the contributions of PrP primary sequence and prion strains to prion transmission barriers and non-PrP factors in prion pathogenesis.

Keywords Prion protein • Prion strain • Transgenic mice • Transmission barrier

11.1 Prion Diseases and Prion Protein (PrP)

Prion diseases, also named transmissible spongiform encephalopathies (TSEs), are a growing family of fatal neurodegenerative diseases that strike humans and many animals (Prusiner 1998; Kong et al. 2004). The prevailing "protein-only" hypothesis postulates that the transmissible pathogenic agent in prion diseases is protein in nature, self-replicating, and requiring no nucleic acids (Prusiner 1982). Numerous experiments have demonstrated that the cellular prion protein (PrP^C) is essential for both prion replication and prion pathogenesis, and that a misfolded PrP aggregate form named PrP^{Sc} is the main (maybe only) essential component of the infectious prion agents, which replicates through PrP^{Sc}-templated conversion of PrP^C.

Q. Kong, Ph.D. (✉)
Department of Pathology, Case Western Reserve University,
11100 Euclid Ave, Cleveland, OH 44106, USA
e-mail: Qingzhong.Kong@Case.edu

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PrP^C is a ubiquitously expressed, cell surface glycoprotein that is glycosylphosphatidylinositol (GPI)-anchored to the outer layer of the cell membrane and highly expressed in the nervous systems, lymphoid tissues, and skeletal muscles. It has also been implicated in several diseases (such as Alzheimer disease, muscle diseases, and cancer) and in many physiological processes (such as neuronal differentiation and neuroprotection, cell adhesion, T cell development and function, and stem cell differentiation) (reviewed by Biasini et al. 2012; Zomosa-Signoret et al. 2008). PrP is encoded by a single copy gene that has numerous polymorphic variants in both humans and animals; some of the polymorphisms are known to modulate prion susceptibility.

Multiple prion "strains" have been observed in humans and animals, characterized by distinctive clinical symptoms, incubation period, histopathology, and specific type and topology of PrP^{Sc} in a specific host species. The basis of prion strains is still not fully established (Collinge and Clarke 2007; Telling 2011), but it is believed that prion strain is encoded in the conformations of PrP^{Sc} (Prusiner 1991; Peretz et al. 2002; Legname et al. 2006), may contain multiple "quasi-species" (Collinge and Clarke 2007), and can undergo mutation and selection (Li et al. 2010). When a prion strain is transmitted to a different host species, the so-called prion transmission "species barrier" is often observed, which manifests as either undetectable infection or variable and prolonged incubation period (including less than 100% transmission) during first passage in contrast to the shortened and less variable incubation period in subsequent passages in the same species. Such barriers could exist even when a prion strain is passaged in animals of the same species but of different PrP genotype or of slightly different genetic background, so the general term "prion transmission barrier" will be used in this chapter.

Transgenic (Tg) mouse models have played many critical roles in prion research and this topic has been reviewed extensively (Baron 2002; Groschup and Buschmann 2008; Telling 2011; Wadsworth et al. 2010; Weissmann and Flechsig 2003). This chapter is not intended to provide an exhaustive review of all prion-related studies involving Tg mice. Instead, I summarize the types of Tg mice used, describe several Tg mouse models and the critical roles they have played in dissecting the factors influencing prion transmission barriers, with a special emphasis on the multifaceted impact of the primary PrP sequences of the prion agent and the host animal. The contributions of host PrP expression level and prion strain to the prion transmission barrier as well as other genes that may participate in prion pathogenesis will also be discussed.

11.2 Creation of Tg Mice

Tg mouse models have played pivotal roles in our understanding of prion diseases, such as establishing the central roles of cellular PrP in both prion replication and prion pathogenesis, modeling various sporadic, genetic and acquired human prion diseased, understanding the basis of prion strains and transmission barriers, uncovering the normal functions of cellular PrP, and evaluating other genes potentially

involved in prion pathogenesis. The Tg mouse models for prion studies are usually created by one of three methods: targeted PrP gene knockout via gene-targeting technology in embryonic stem cells, targeted PrP gene replacement (knock-in) in embryonic stem cells, and conventional transgenesis via chromosomal integration of a wild-type or mutated PrP gene from the same or different species after pronuclear injecting of a PrP transgene DNA construct into individual fertilized eggs (see Gama Sosa et al. 2010 for a general review on various Tg mouse techniques). The few reported PrP knock-in mouse models (Kitamoto et al. 2002; Moore et al. 2005; Jackson et al. 2009) have the unique advantage of ensuring nearly authentic level and tissue profile of the Tg PrP expression, but they will not allow variation of the level and profile of transgene PrP expression. The conventional Tg technology is more versatile for a number of reasons. It can generate from one transgene construct many unique Tg mouse lines with different level and tissue profile of transgene PrP expression because the chromosomal transgene integration site is relatively random and the copy number of the integrated transgene can vary hugely from one line to another. It also allows the use of specific promoters that confer tissue/cell specific or developmentally regulated transgene expression to more precisely control the location, timing, and amount as well as other regulations (such as response to a specific stimulus or chemical). As discussed in detail below, the PrP knockout mice and to a lesser extent, the PrP knock-in mice have played significant and unique roles in prion research, whereas most of the Tg mouse models for prion studies were established with the conventional transgenesis technique.

11.3 Influence of Donor (Prion) and Host PrP Primary Sequences

One of the most important contributions of Tg mouse models is demonstrating the requirement of PrP^C in prion replication and pathogenesis. PrP knockout mice had been generated by targeted gene knockout technology in several laboratories (Büeler et al. 1992; Manson et al. 1994a; Sakaguchi et al. 1995; Moore et al. 1995; Rossi et al. 2008), which revealed that PrP^C is not essential for viability and the PrP knockout mice with undisturbed doppel expression appear almost completely normal (Büeler et al. 1992, Manson et al. 1994a). Prion transmission experiments in these PrP knockout mice invariably failed to lead to infection (Büeler et al. 1993; Prusiner et al. 1993; Manson et al. 1994a; Sailer et al. 1994; Sakaguchi et al. 1995) and reintroduction of functional PrP expression via a transgene restored the susceptibility (Prusiner et al. 1993), proving unequivocally that PrP^C expression is required for prion replication. The evidence for the requirement of host PrP^C expression in prion pathogenesis mainly came from neurografting (Brandner et al. 1996) and conditional knockout experiments (Mallucci et al. 2007). When brain tissues from PrP-overexpressing mice were grafted to the brain of PrP knockout mice, after intracerebral prion inoculation, the prion pathology was found to be limited to the grafted PrP-expressing tissues; in contrast, there was little prion pathology in the

other brain regions despite the presence of significant amount of PrP^{Sc} (Brandner et al. 1996). In addition, when the neurografted mice were challenged by intraperitoneal prion inoculation, no pathology was detected in the grafted tissue, suggesting the requirement of extracerebral PrP^{C} expression for neuroinvasion of peripherally inoculated prions (Brandner et al. 1996). These results indicate convincingly that PrP^{C} expression is essential for prion pathogenesis. This conclusion is reinforced by more recent experiments (Mallucci et al. 2002, 2003, 2007) using the Cre–Lox conditional knockout system (reviewed by Feil 2007). A Tg mouse line (NFH-Cre/tg37) was created by breeding the tg37 line expressing a PrP transgene flanked by loxP sites with the NFH-Cre mice expressing the Cre DNA recombinase gene under the developmentally regulated NFH promoter, which initiates Cre expression in neurons 9–10 weeks after birth to knock out neuronal PrP transgene expression (Mallucci et al. 2002). When the tg37 mice were inoculated with the RML prion strain at 1 week of age, the animals started to display behavior deficits and early spongiosis in the brain at 9 weeks and reached terminal stage at 14 weeks. In similarly prion-inoculated NFH-Cre/tg37 mice, the animals displayed behavior deficits and early spongiosis in the brain at 9 weeks of age as expected, but soon after the spongiosis is reversed and behavior deficits disappeared (Mallucci et al. 2003, 2007). These pivotal experiments not only demonstrate the requirement for host neuronal PrP^{C} expression in prion pathogenesis but also prove in principle that prion pathology can be reversed at early stages through knocking out neuronal PrP expression, suggesting that reducing neuronal PrP expression is an effective therapeutic strategy for prion diseases.

Tg mouse models are also instrumental in establishing that the primary PrP sequences of the prion donor and recipient host animals are critical factors for the strength of prion transmission barrier. Earlier prion transmission studies were often carried out in nontransgenic wild-type rodents (mice, hamsters, and guinea pigs), where highly variable transmissions were often observed depending on the source of the prion inoculum. Wild-type mice are usually poor hosts to prions from humans and other species. In 1989, the Prusiner group reported the first Tg mice expressing hamster PrP, which were readily infected by hamster prions (Scott et al. 1989). In 1994, the Prusiner group showed that Tg mice expressing chimeric human–mouse PrP [Tg(MHu2M)] in the presence of endogenous mouse PrP are highly susceptible to three human CJD isolates (Telling et al. 1994). They also showed that Tg(HuPrP) mice expressing human PrP in the presence of endogenous mouse PrP were poorly susceptible to the CJD isolates (Telling et al. 1994), but ablation of the mouse PrP gene made the Tg(HuPrP) mice highly susceptible to CJD prions (Telling et al. 1995), indicating that replacement of mouse PrP with human PrP in Tg mice breaks the resistance to human prions and the endogenous mouse PrP^{C} interferes with the propagation of CJD prions. Subsequent creation and testing of Tg mice expressing PrP from other species (cattle, sheep/goat, cervids, pig) in many laboratories further confirmed that Tg expression of PrP from a certain species in mice in the absence of endogenous mouse PrP renders the mice susceptible to homologous prions (e.g., Buschmann et al. 2000; Vilotte et al. 2001; Browning et al. 2004; Kong et al. 2005), establishing the central role of PrP primary sequence in prion transmission barriers. However, there appear to be a few exceptions. For example, bank vole is highly susceptible to prions from humans

(Nonno et al. 2006) and many other species despite significant differences in their primary PrP sequences. It appears likely that bank vole PrP^{C} is inherently prone to adopting misfolded PrP^{Sc} conformations, which makes the homology with PrP^{Sc} less important. This notion is supported by the observation that Tg mice overexpressing wild-type bank vole PrP (TgBVPrP) develop spontaneous prion disease that is transmissible to both wild-type mice and Tg(BVPrP) (Watts et al. 2012).

Tg mice expressing polymorphic or modified PrPs showcased how even seemingly small changes in the primary PrP structure of the host animal can dramatically influence its susceptibility to specific prion strains. The PrP codon 129M/V polymorphism is common in human populations, and it is known to have a huge impact on the susceptibility to not only exogenous prion infections but also to the risk of developing sporadic CJD (reviewed by Kong et al. 2004). One example is variant CJD (vCJD) caused by BSE infection in humans. All the 200-plus clinical cases of vCJD detected so far are homozygous for Met at the PrP codon 129. This dramatic preference of classic BSE prion for the human PrP-129MM genotype is confirmed by transmission of BSE prion in Tg mice expressing human PrP-129M, human PrP-129V, or human PrP-129MV, although these Tg mouse studies also suggest that individuals with PrP-129VV or PrP-129MV genotypes may not be completely resistant to the BSE prion (Asante et al. 2002, 2006; Wadsworth et al. 2004). Tg mice carrying the single amino acid P101L mutation associated with the inheritable human Gerstmann–Sträussler–Scheinker syndrome (GSS) cases also altered the incubation times for various prion strains (Manson et al. 1999). In addition, the so-called heterozygous inhibition has been observed in Tg mouse models expressing two types of PrP^{C} (Hizume et al. 2009; Kobayashi et al. 2009).

Moreover, Tg mice expressing modified PrP revealed a structure region critical for cross-species prion transmission barrier. The β2–α2 loop region of PrP^{C} is less conserved among different species, which can be roughly classified into two groups: those with a rigid β2–α2 loop and those with a disordered β2–α2 loop. Using transgenic mouse models expressing PrP with rigid or disordered β2–α2 loop, Christina Sigurdson and her colleagues found that the transmission barrier is generally weaker when the transgenic host and the prion inoculum contain PrPs with the same type of β2–α2 loop and stronger when their β2–α2 loops do not match (Sigurdson et al. 2010).

11.4 Contribution of Host PrP Expression Level

The host PrP^{C} expression levels also affect prion transmission barrier: higher PrP^{C} levels usually correspond to lower transmission barriers, which is not unexpected given that host PrP^{C} is the substrate for PrP^{Sc} replication. The first experimental evidence for this principle came from the Prusiner lab, where the wild-type Syrian hamster PrP (SHaPrP) was expressed at various levels in the Tg(SHaPrP) mouse lines and the incubation period of a hamster prion strain was found to be inversely proportional to the level of SHaPrP in the mouse brain (Scott et al. 1989; Prusiner et al. 1990). Similar results were later obtained using prion strains from other

species and Tg mice expressing homologous PrP from those species. Westaway et al. (1991) found that Tg mice overexpressing the mouse PrP gene exhibit reduced incubation time when challenged with the Chandler scrapie isolate. Also, the hemizygous PrP knockout mice (*Prnp*$^{+/o}$) expressing half the amount of PrP of wild-type mice showed delayed onset of disease (Prusiner et al. 1993; Büeler et al. 1994; Manson et al. 1994b), whereas the Tga20 mice overexpressing the mouse PrP gene had a much shorter incubation time (Fischer et al. 1996). The increased susceptibility of Tg mice overexpressing PrP from a species is therefore used to shorten the incubation time of prions from the same species to save time and cost in laboratory studies. Moreover, Tg mice overexpressing PrP have also been utilized to detect weak cross-species prion transmissions. For example, the classical BSE strain led to detectable but poor infection in Tg mice overexpressing HuPrP (Scott et al. 1999; Asante et al. 2002, 2006; Wadsworth et al. 2004), but it failed to infect the knock-in mice that express HuPrP at wild-type mouse level (Bishop et al. 2006). We also found that both the classical BSE strain and the atypical H-type BSE strain resulted in poor but detectable infection in the Tg40h mice expressing HuPrP-129M at 2× wild-type level, but not in the Tg40 mice expressing HuPrP-129M at 1× wild-type level (Q Kong et al. unpublished data). The Prusiner group (Tremblay et al. 1998) reported the dramatic impact of host PrP-expressing levels on prion transmission using tetracycline-regulated Tg mice (reviewed by Stieger et al. 2009). The Tg mice normally express very high levels of mouse PrP and became ataxic only 50 days after inoculation with the RML prions, but suppression of PrP^{C} expression by >90% with oral doxycycline completely prevented clinical prion disease despite the presence of low levels of PrP^{Sc}. These findings prove that the transgenic PrP expression level has a dramatic impact on prion transmission barrier and this factor must be taken into account when Tg mouse models are used to evaluate prion transmission species barriers. Furthermore, reduction of host PrP expression levels in the brain appears to be a viable strategy to treat prion diseases as evidenced by RNA interference experiments in mice (Kong 2006; Pfeifer et al. 2006; White et al. 2008).

11.5 Effect of Prion Strain

The first transgenic evidence for the influence of prion strain on transmission barrier was reported by Peretz et al. (2002). They showed that transmission of the hamster scrapie strain Sc237 in the Tg(MH2M) mice expressing chimeric hamster/mouse PrP gene was poor and led to a new prion strain with changed conformational stability and disease phenotype; in contrast, transmission of the DY (drowsy) hamster prion strain in the same Tg(MH2M) mice had no barrier and the resulting prion maintained the characteristics of the original DY strain. More recently, Jean Manson's group reclassified several distinct human sporadic CJD isolates belonging to the six subtypes of sporadic CJD (sCJD) (MM1, MM2, MV1, MV2, VV1, and VV2) as described by Parchi et al. (1996) using their knock-in mouse models expressing HuPrP-129M, HuPrP-129V or both HuPrP-129M and HuPrP-129V (Bishop et al. 2010). They found that these six

sCJD subtypes actually represent four human prion strains that are different in transmissibility, incubation time, histological lesion profile, and types and deposition patterns of PrP^{Sc} (Bishop et al. 2010). For example, the sCJDMM2 subtype (the $M2^{CJD}$ strain) has zero to very poor transmission in all three knock-in mouse models, whereas the MM1/MV1 subtypes (the $M1^{CJD}$ strain) are at least moderately transmissible in all mouse models. Strain-dependent barriers for prion transmission are also observed with prion strains from mouse and cattle in Tg mouse models expressing respective PrPs.

11.6 Non-PrP Factors Involved in Prion Diseases

Many non-PrP proteins are suspected to play a role in prion pathogenesis. They either colocalize with PrP^{C}, participate in/are associated with Alzheimer's disease, are elevated during prion disease, or function in PrP-mediated signaling, PrP glycosylation, PrP^{C} processing or protein maintenance. Tg mice where the respective gene of the suspected protein is knocked out or overexpressed are effective tools to assess the involvement of such candidate genes. Tamgüney et al. (2008) presented a comprehensive study using this strategy to examine 20 such candidate genes, including amyloid precursor protein (APP), amyloid-beta precursor-like protein (APLP2), human ApoE (ε3 and ε4 alleles), interleukin-10, interleukin-1 receptor type I (IL-1R1), tumor necrosis factor (TNF-α), transforming growth factor-β1 (TGF-β1), chemokine (C-C motif) receptor 2 (CCR2), chemokine (C-C motif) receptor 5 (CCR5), methionine sulfoxide reductase A and B (MsrA and MsrB), human SOD-1, human Hsp70, mannosdie-b1,4-N-acetylglucosaminyltransferase III (Mgat3), caveolin-1, Fyn kinase, receptor protein tyrosine phosphatase-α (RPTPα), doppel (Dpl), and CD9. However, most genes examined appear to have no significant impact and only ablation of APP or IL-1R1 and overexpression of human SOD-1 were found to slightly increase the incubation time (13–19 %). Other PrP-interacting proteins have also been studied. Plasminogen was reported to bind and cleave PrP^{C} (Kornblatt et al. 2003). However, knocking out the mouse plasminogen gene has no major effect on the survival of scrapie-infected mice (Salmona et al. 2005). The 36-kDa/67-kDa laminin receptor (LRP/LR) was implicated as the cell surface receptor for both PrP^{C} and PrP^{Sc} (Gauczynski et al. 2001, 2006; Hundt et al. 2001) and its expression is required for PrP^{Sc} propagation in scrapie-infected neuronal cells (Leucht et al. 2003). Expression of a mutant LRP interfered with PrP^{Sc} propagation in cultured neuronal cells (Vana and Weiss 2006) and significantly prolonged the incubation time and reduced PrP^{Sc} accumulation in Tg mice (Pflanz et al. 2009), suggesting that LRP facilitates PrP^{Sc} replication in vivo.

Factors affecting the clearance of PrP^{Sc} also influence prion pathogenesis. Knocking out Mfge8 (milk fat globule epidermal growth factor 8, which mediates engulfment of apoptotic bodies by phagocytes) was found to result in accelerated prion disease, excessive PrP^{Sc} accumulation and increased prion titers (Kranich et al. 2010). Safar et al. (2000) also reported a linear correlation between the protease-sensitive PrP^{Sc} fraction and the length of incubation time and suggested

that different incubation times of various prion strains may arise predominantly from distinct rates of PrP^{Sc} clearance. It can be inferred that a species with a powerful PrP^{Sc} clearance mechanism will be more resistant to prion infection. On the other hand, the effectiveness of the PrP^{Sc} clearance mechanism of an animal could be prion strain dependent and influenced by the age and other physiological or pathological factors. This consideration could partially explain the age-dependent nature of the onset of prion diseases.

More recently, sustained translational repression by phosphorylated translation initiation factor eIF2α is also implicated in prion pathogenesis, because in prion-inoculated mice, transgenic overexpression of an eIF2α-specific phosphatase significantly prolonged survival, whereas treatment with an inhibitor of dephosphorylation of phosphorylated eIF2α shortened survival (Moreno et al. 2012).

11.7 Conclusions

The numerous transgenic mouse models have been essential to our current knowledge on the nature and replication of the prion agents and prion strains, other factors/genes involved in prion pathogenesis, as well as the basis of prion transmission barrier. Development and application of novel transgenic mouse models, complemented by cell culture models of prion replication and cell-free protein misfolding cyclic amplification (PMCA) and other related in vitro PrP^{Sc} replication and detection techniques, will lead to a broader and deeper understanding on all aspects of prion diseases and prion agents, including the development of effective prevention and therapeutics for prions.

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