

How do prion diseases work?

# 朊病毒疾病将如何发展?

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**摘要** 疯牛病是传染性海绵状脑病(朊病毒病)的一种, 1985年在英国暴发的疯牛病引起了全世界的关注. 发生疯牛病的分子机制是疯牛病毒诱导细胞型朊蛋白的构象发生变化, 从富含 $\alpha$ -螺旋的细胞型朊蛋白转变为富含 $\beta$ -折叠的疯牛病毒, 导致这种构象变化的原因目前仍然未知. 这类传染性的神经退行性疾病目前仍然没有有效的治疗方法. 虽然禁止肉骨粉作为动物饲料明显地抑制了疯牛病的进一步流行, 但是羊瘙痒病、水貂传染性脑炎和鹿慢性消耗性疾病等朊病毒疾病的流行病学表明朊病毒已经并将持续存在于自然界, 而和人类健康息息相关. 除朊病毒病外, 多种神经退行性疾病如阿尔兹海默病、帕金森病、亨廷顿舞蹈病等致病的原因都是由蛋白质异构引起的, 因此阐明朊病毒疾病的致病机制对于其他神经退行性疾病的研究有重要的借鉴意义. 本文回顾了几大类传染型朊病毒疾病的发生历史和现状, 依据朊病毒的发生及传播特性指出朊病毒疾病不可能被根除并存在暴发的潜在可能.

**关键词** 朊病毒疾病, 传染性海绵状脑病, 疯牛病, 羊瘙痒病, 朊病毒, 朊病毒蛋白, 蛋白质构象变化

朊病毒病(prion diseases)也称传染性海绵状脑病(transmissible spongiform encephalopathy, TSE), 是由朊病毒引起的可感染人和动物的致死性神经退行性疾病. 典型的朊病毒病包括人的克雅氏病(Creutzfeldt-Jakob disease, CJD)、吉斯特曼斯特劳斯综合征(Gerstmann-Sträussler-Scheinker syndrome, GSS)、致死性家族性失眠症(fatal familial insomnia, FFI)、散发型致死性失眠症(sporadic fatal insomnia, SFI)、库鲁病(Kuru)、变异型克雅氏病(new variant Creutzfeldt-Jakob disease, vCJD)、牛传染性海绵状脑病(bovine spongiform encephalopathy, BSE)或称疯牛病和羊瘙痒病(scrapie)等. 人类朊病毒病的发病率非常低, 为每年每百万人1~3例. 根据传播途径的差异, 朊病毒病可以分为散发型(sporadic)、遗传型(genetic)和感染型(infectious)三大类. 其中遗传型朊病毒病是指由人

或动物本身编码细胞型朊蛋白(cellular prion protein, PrP<sup>C</sup>)的基因(PRNP)存在致病性突变引起的, 发病率约为10%~15%; 传染型朊病毒病是指由含朊病毒(PrP<sup>SC</sup>)的物品感染所致, 发生率低于1%; 散发型朊病毒病是指病原不明确的朊病毒病, 发生率约85%. 值得注意的是, 任何一种朊病毒病都具有潜在传染性.

## 1 致病机理

引起动物和人类朊病毒病的病原为朊病毒(prion), 该病毒中检测不到足够量或足够长的能编码遗传信息的核酸. 构成朊病毒的主要成分是蛋白质聚集体<sup>[1]</sup>, 可能含有少量的脂类或糖类<sup>[2]</sup>. 朊病毒感染主要引起中枢神经细胞的死亡, 感染必要条件是中枢神经细胞表达朊蛋白, 这是一个和朊病毒具有相同氨基酸序列但不同二级构象的蛋白质. 朊病毒

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不溶于水且对蛋白酶K具有部分抗性,研究发现损伤核酸的方法都不能消除朊病毒的感染性,而朊蛋白溶于水且易被蛋白酶K消化,这是区分朊病毒和朊蛋白的重要生化手段。

编码朊蛋白的 *PRNP* 基因位于人类染色体的 20p13 上,而小鼠 (*Mus musculus*) 的 *prnp* 基因位于 2F2 上。从进化的角度来看,朊蛋白基因出现于所有的脊椎动物中,并在哺乳动物中高度保守。朊蛋白在动物组织中广泛分布,尤其在中枢神经系统的神经元、心脏、淋巴系统、消化道上皮和肌肉等部位高表达。朊蛋白的生物合成较为复杂,其氨基端具有效率不高的入内质网信号肽,在羧基端具有糖基磷脂酰肌醇锚信号肽。氨基端的信号肽进入内质网后被切除,而羧基端的信号肽在内质网中被糖基磷脂酰肌醇锚生物合成酶识别后被置换。除蛋白质羧基和氨基端的信号肽需要被切除外,朊蛋白还会形成分子内二硫键及被 N-链接糖基修饰。完成翻译后修饰的朊蛋白最终经由高尔基外侧网络分泌到细胞膜外表面并利用糖基磷脂酰肌醇锚定位于脂筏中。朊蛋白的具体生理功能目前并没有确定,但有研究表明该蛋白参与了细胞的多种生理过程,包括细胞的迁移和黏附。朊蛋白是整合素黏连复合体中的成分<sup>[3]</sup>,虽然 *prnp* 敲除的小鼠没有明显的生长发育的缺陷,但 *prnp* 敲除的斑马鱼 (*Danio rerio*) 却表现出细胞迁移缺陷导致的胚胎死亡<sup>[4]</sup>。研究表明,朊病毒本身并没有明显的细胞毒性,朊病毒感染 *prnp* 敲除的小鼠并不引起小鼠的朊病毒病<sup>[5]</sup>。只有当小鼠中枢神经细胞表达朊蛋白,朊病毒才引起小鼠神经退行性病变。在这个过程中,朊病毒诱导朊蛋白发生构象变化,由  $\alpha$  螺旋为主的朊蛋白转变为  $\beta$  折叠为主的朊病毒从而导致了神经细胞的死亡,具体的机制仍然不明确。此外,朊病毒具有明显的种属屏障和毒株差异性,即不同种属的动物感染朊病毒后,潜伏期长短、临床表现、朊病毒生化特点等均不相同,同时感染同一种属的不同朊病毒毒株亦存在上述差异性。

## 2 动物传染型疯牛病发展概况

### 2.1 牛传染性海绵状脑病

又称为疯牛病 (mad cow disease), 1985 年发生于英国的世界上第一例牛传染性海绵状脑病 (bovine spongiform encephalopathy, BSE) 导致了极大的恐慌

并使该病进入公众视野<sup>[6]</sup>。此后全世界有近 20 万头牛被确诊发生了牛传染性海绵状脑病,估计感染的病牛超过 2 百万头<sup>[7]</sup>。典型的牛传染性海绵状脑病病理特征包括中枢神经系统的海绵状空泡、朊病毒聚集体的沉积和星状胶质细胞的增生。牛传染性海绵状脑病的潜伏期一般为 2~5 年,在临床症状出现后病牛一般在 2 周到 6 个月内死亡。流行病学调查表明病牛的牛奶、精液和胚胎等检测不到朊病毒且不具有传染性,也没有疯牛病种内自然传播的报道。但相比于未感染牛,病牛的后代更加容易再发牛传染性海绵状脑病<sup>[8]</sup>。

除引起经典的牛传染性海绵状脑病的朊病毒株外,还存在能引起非典型性牛传染性海绵状脑病的 H-型和 L-型两种毒株。和典型性疯牛病病毒相比, H-型毒株在有限蛋白酶 K 消化的条件下无糖基组分分子量较高,而 L-型毒株的主要成分是单糖基修饰的,无糖基组分的分子量较低。非典型性牛传染性海绵状脑病往往是对倒地牛进行病理检测时才确诊<sup>[9,10]</sup>。由 L-型病毒引起的非典型性疯牛病的脑中,可以检测到淀粉样蛋白斑。疯牛病病毒的最早来源目前仍然不确定,散发型或遗传型朊病毒进入肉骨粉是导致牛传染性海绵状脑病发生的可能原因<sup>[11~16]</sup>。在英国的牛传染性海绵状脑病流行期间,从外国引进到英国的一些牛科的反刍动物也被证实发生牛传染性海绵状脑病,虽然致病原因归于这些动物食用了含牛朊病毒的肉骨粉,这些患病动物的临床症状和疾病进程却明显不同于牛传染性海绵状脑病和羊瘙痒病<sup>[17,18]</sup>。牛朊蛋白基因多态性对于疯牛病病毒感染存在一定的影响,这些多态性基因包括 *E211K*, *PRNP* 上游启动子区的 23 个碱基对的突变和位于第一个内含子中 12 个碱基对的突变<sup>[19~21]</sup>。

### 2.2 羊瘙痒病

羊瘙痒病 (Scrapie) 是最早被发现和确认的一类朊病毒病,绵羊 (*Ovis aries*)、山羊 (*Capra aegagrus hircus*) 等都可以感染此病,发病率可达 0.12%。和牛传染性海绵状脑病一样,羊瘙痒病的最初感染源未知。羊瘙痒病于 1732 年在欧洲就已被发现<sup>[22]</sup>,由于一直没有传染到人而没有引起广泛重视。典型的羊瘙痒病病理特征包括中枢神经系统的海绵状空泡、朊病毒聚集体的沉积和星状胶质细胞增生,临床表现为挠痒导致的皮肤损伤、唇动和抽搐性崩溃等,而非

典型的羊瘙痒病临床表现为共济失调。除在扁桃体、脾脏、淋巴系统、肌肉等组织和器官可以检测到羊朊病毒外,在病羊的排泄物和分泌物中也存在可以水平传播的朊病毒,该病的年病死率为3%~5%,但是在一些羊群中年死亡率可以高达20%<sup>[23]</sup>。除个体间水平传播外,也可能存在母婴间垂直传播途径<sup>[24,25]</sup>。绵羊朊蛋白基因(*PRNP*)的多态性和羊瘙痒病的易感性存在一定的关联性,Q171R多态性对羊瘙痒病的感染具有很强的抗性而A136V多态性则极易感染。通过多年的努力,欧洲联盟国家建立了基于绵羊朊蛋白基因的三位点培育体系,即A136V, R154H和Q171R体系来确定对羊瘙痒病的易感性,其中ARR/ARR纯合子具有最高的抗羊瘙痒病的能力。由于这些纯合子绵羊的产量、生长、繁殖和健康都和其他羊没有明显的差异<sup>[26]</sup>,因此欧洲联盟在2001年开始培育有抗性基因的羊(commission regulation EC 999/2001 and commission decisions 2002/1003/EC3和2003/100/EC4)。类似地,山羊朊蛋白基因(*PRNP*)的多态性I142M, H143R, N146S/D, R154H, R211Q和Q222K也对羊瘙痒病的感染表现出明显的抗性。

### 2.3 鹿慢性消耗病

最早于1967年发现并于1996年首先在加拿大被报道<sup>[27]</sup>,随后在美国14个州,加拿大2个省和韩国都有报道。鹿慢性消耗病(Chronic Wasting Disease, CWD)在鹿(*Cervidae*)种群中的发病率可以从0.1%到50%,甚至100%。与牛传染性海绵状脑病和羊瘙痒病一样,引起鹿慢性消耗病的病原来源还不清楚。鹿慢性消耗病最重要的病理特征是出现在迷走神经背运动核的神经空泡,星形细胞肥大和增生。鹿慢性消耗病的潜伏期一般是16个月到5年,出现症状的鹿一般在1年内死亡。自然感染的鹿种群中可能存在超过一种引起鹿慢性消耗病的病毒<sup>[28]</sup>。与羊瘙痒病一样,流行病学和实验证据表明鹿慢性消耗病可以在鹿之间水平传播,与病鹿接触或生活在鹿朊病毒污染的环境中,健康鹿可以被感染<sup>[28~31]</sup>。此外,在鹿中还存在母婴间垂直传播的可能性<sup>[32,33]</sup>。虽然实验证据表明,鹿可以通过口腔途径感染鹿慢性消耗病,但是自然种群中鹿的感染途径并不明确<sup>[34,35]</sup>。当健康鹿存在口腔溃疡或鼻腔暴露在感染性的朊病毒气雾中时,感染性会增强<sup>[36,37]</sup>。目前的流行病学和实验证据表明鹿慢性消耗病病毒不能自发传染给人类、牛和羊,但是可以

传染其他种类的鹿<sup>[31,34,35,38]</sup>。鹿的朊蛋白基因(*PRNP*)的多态性S96G, M132L和S225F也表现出较强的抵抗鹿慢性消耗病感染的能力,这为培育抗鹿慢性消耗病鹿提供了理论基础<sup>[28]</sup>。

### 2.4 传染性水貂脑病

最早于1947年在美国威仕康星州和明尼苏达州的圈养水貂(*Mustela vison/lutreola*)中发现,其后于21世纪60和70年代持续暴发,最近的暴发时间是1985年。除美国外,加拿大、芬兰、德国和前苏联也发生过该病的暴发。引起该病的病原不明确,最早推测是羊瘙痒病病毒,但是L-型牛朊病毒可能是该病的真正元凶<sup>[39]</sup>。除引起L-型疯牛病的牛朊病毒外,经典的牛朊病毒也可以通过口腔传染给水貂,但是引起相对温和的而非攻击性表型。传染性水貂脑病(transmissible mink encephalopathy, TME)可以通过同类残食或水貂间相互撕咬而传染。传染性水貂脑病通常发生在成年水貂中,疾病暴发时死亡率可以高达60%~90%,甚至100%。目前该病没有母婴间垂直传播的报道,暴露在传染性水貂脑病污染的环境中也没有发生感染的报道。自然发生的传染性水貂脑病潜伏期一般是6~12个月,感染的水貂随后在2~8周死亡<sup>[38]</sup>。患病的水貂早期表现为进食和吞咽困难,晚期表现出强攻击性、共济失调等行为,而且经常将粪便排污在窝中。除种内传播外,条纹臭鼬(*Mephitis mephitis*)、雪貂(*Mustela putorius furo*)、石貂(*Martes foina*)、羊、仓鼠(*Cricetidae*)和除人外的多种灵长类,如恒河猴(*Macaca mulatta*)等可以感染传染性水貂脑病。用传染性水貂脑病病毒实验感染仓鼠的研究表明传染性水貂脑病至少有两个毒株:一种引起嗜睡症(drowsy),而另一种引起亢奋症(hyper)。

### 2.5 猫海绵状传染性脑病

发生于家猫(*Felis catus*)和圈养的猫科动物中,从20世纪90年代开始,已经有超过100只家猫和19只野生被圈养的猫科动物,包括狮子(*Panthera leo*)、美洲虎(*Panthera onca*)等出现了该病。所有的猫海绵状传染性脑病(feline spongiform encephalopathy, FSE)都发生在两岁以上的猫科动物,家猫在临床症状出现后3~8周死亡而猎豹在临床症状出现8~10周死亡<sup>[38]</sup>。由于大多数的猫海绵状传染性脑病发生和牛传染性海绵状脑病的发生存在时间上的高度重合,

因此推测该病的发生是由于这些猫科动物食用了含有牛朊病毒的肉骨粉导致的。除肉骨粉作为猫海绵状传染性脑病水平传播的可能病原外,圈养的猎豹可能发生母子间垂直传播<sup>[40]</sup>。家猫也可能患上非猫海绵状传染性脑病的朊病毒病,1998年在意大利发生了一例家猫和饲养者同时患朊病毒病的例子,该病例中家猫的病理特征不同于猫海绵状传染性脑病,而饲养者的病理特征显示为散发型朊病毒病。导致这例二分型疯牛病发生的原因目前并不明确<sup>[41]</sup>。

### 3 人类传染性朊病毒病发展概况

引起人类朊病毒病的病原为朊病毒,依据毒株差异散发型克雅氏病毒株可以分为M1, V1, M2, V2, 另外还存在散发型致死性失眠症病毒,家族性致死性失眠症毒株,和两种从吉斯特曼斯特劳综合征来源的毒株共8种<sup>[42~46]</sup>。此外,还存在能致病的蛋白酶K敏感朊病毒和淀粉样沉淀脑病朊病毒<sup>[47,48]</sup>。导致遗传性朊病毒的点突变目前报道有50种<sup>[49]</sup>,其中4种点突变导致的神经退行病变的临床表征类似阿尔兹海默病(Alzheimer disease, AD)<sup>[50,51]</sup>。导致遗传性朊病毒病的大多数突变位点发生在PRNP羧基端,但是位于氨基端的30余种8肽重复区的缺失或插入突变也会导致朊病毒病<sup>[49]</sup>。和PRNP点突变可能导致阿尔兹海默病一样,位于第82位氨基酸附近的8肽重叠区的缺失也可能产生类似阿尔兹海默病的临床表现<sup>[52]</sup>。人类历史上因传染引起的朊病毒病主要包括库鲁病、医源性克雅氏病和新变异型克雅氏病。

#### 3.1 库鲁病

第一例库鲁病据报道可能于1910年发生在亚洲的巴布亚新几内亚<sup>[53]</sup>,在当地造成该病流行的重要原因是近亲相食(endocannibalism)。自20世纪60年代这个风俗被禁止后,该病发生率急速下降<sup>[54]</sup>。极少数库鲁病患者直到2004年4月仍然存活,这些患者长期无临床症状存活的原因可能是因为他们的PRNP基因为129甲硫氨酸/缬氨酸杂合子。该基因型对朊病毒的感染具有较高的抗性或感染后可具有较长的感染潜伏期<sup>[55]</sup>。

#### 3.2 医源性克雅氏病

第一例医源性克雅氏病(iatrogenic CJD)于1974年由Duffy等人<sup>[56]</sup>报道。产生医源性克雅氏病的原因是器官供体或医疗器械被朊病毒污染,包括朊病毒

污染的用于移植的角膜、电极插片、人类生长激素和血液制品等。随着传染源的确定,人类生长激素生产的规范化及医疗器械消毒的严格化,医源性克雅氏病的发生也明显下降,到2016年全世界确诊的医源性克雅氏病患者为492例<sup>[57]</sup>。

#### 3.3 新变异型克雅氏病

1996年首次在英国确认发生,截止到2015年12月,该病在全球共发生228例,其中英国发生177例,英国以外其他11个国家发生51例。该病的发病高峰期是2000年,共计发生28例。随后新变异型克雅氏病发病率下降,2012~2013年,每年只发生1例<sup>[58]</sup>。引起新变异型克雅氏病的主要原因是食用了含朊病毒的牛肉,另有4例因输血而引发新变异型克雅氏病。新变异型克雅氏病早期表现精神症状,约持续6个月,如抑郁,焦虑不安。随后患者快速表现出神经症状,如共济失调等<sup>[59,60]</sup>。相较于散发型克雅氏病,新变异型克雅氏病的患者死亡年龄中位数明显下降,但是临床症状出现后患者平均存活14个月,远高于散发型克雅氏病的4个月。与动物的朊病毒病一样,实验动物结果和流行病学调查表明人朊蛋白基因多态性对朊病毒的易感性有很大的影响,易感性从高到低是129甲硫氨酸纯合子>129甲硫氨酸/缬氨酸杂合子>129缬氨酸纯合子。虽然在一例因输血导致的非典型新变异型克雅氏病患者中患者朊蛋白基因的基因型是129甲硫氨酸/缬氨酸杂合子,但临床检验发现其他新变异型克雅氏病的患者的朊蛋白基因型都是129甲硫氨酸纯合子。由于欧美高加索人种朊蛋白基因的129甲硫氨酸纯合子比例为42%,而新变异型克雅氏病患者朊蛋白基因型的129甲硫氨酸纯合子比例接近100%,这个结果表明129甲硫氨酸纯合子对朊病毒易感。除典型的新变异型克雅氏病外,英国等疯牛病流行过的国家存在无临床症状的新变异型克雅氏病,产生的原因在于朊蛋白PRNP基因多态性中的129甲硫氨酸/缬氨酸杂合子和129缬氨酸纯合子对朊病毒具有较强的抗性而且欧美高加索人种中这两种基因型的比例高达47%和11%。由于抗性的存在,这些基因型的患者存在较长时间的无临床症状期。根据2004年的第一次报道,无临床症状新变异型克雅氏病发生的可能性高达每百万人中49~692例<sup>[61]</sup>,其后的多次研究获得了类似的结论<sup>[8,62~64]</sup>。由于存在无临床症状新变异型克雅氏病,对这类患者做过手术



的器械如果消毒处理未能严格按照朊病毒消毒程序,或者误输这些患者献的血或器官移植等都可能引发次生性新变异型克雅氏病. 虽然最新10年跟踪调查结果表明,尚没有出现新的因输血导致的新变异型克雅氏病<sup>[65]</sup>,但是输血导致新变异型克雅氏病仍然是英国国会质询的焦点问题之一(Parliamentary Select Committee on Science and Technology, MPs launch inquiry on blood, tissue and organs screening following vCJD fears, 2013).

## 4 朊病毒疾病的未来和发展趋势

### 4.1 动物性朊病毒病不能在自然界被消灭

阻断疯牛病的传染源是疯牛病防治取得卓越成效的原因. 由于肉骨粉的禁用,全世界发生的动物性朊病毒病显著下降;禁止近亲相食极大地控制了库鲁病;欧美国家对于死亡患者的朊病毒病排查,明显地减少了医源性克雅氏病的发生. 从动物性朊病毒病发生的历史来看,羊瘙痒病、鹿慢性消耗性疾病和水貂传染性脑病首次发生的病原来源都不清楚. 除疯牛病外,其他动物首次发病时都不存在含朊病毒肉骨粉作为饲料的可能性. 因此,朊病毒病的感染途径在自然条件下就已经存在,例如,在远离鹿慢性消耗性疾病疫区的美国其他地方也发生了该病<sup>[66]</sup>. 由于朊病毒可以结合土壤颗粒,其感染性在这种状态下可以保持多年并且感染效率可能更高<sup>[67~69]</sup>,因此,动物的散发型或遗传型朊病毒可能来源于黏附在土壤颗粒上朊病毒. 存在于自然环境中的这些朊病毒使得消灭动物性朊病毒疾病变得不可能. 朊病毒病的自然传播还存在另一种可能性,虽然朊病毒在某些物种间传播屏障可以防止朊病毒的跨种传播,但是朊病毒可以在其他不同的物种间传播从而可以产生新的毒株,这种新的毒株有可能克服物种间朊病毒之前存在的种间屏障<sup>[70~73]</sup>. 例如,种间屏障导致朊病毒X不能从物种A传到B,但是朊病毒X可以从物种A先传到物种C而形成朊病毒Y,而朊病毒Y就可

能从物种C传到物种B.

### 4.2 人类朊病毒病将伴随人类存在

即使典型的动物性朊病毒病传染途径被阻断,非典型动物性朊病毒病传染到人的可能性仍然存在. 由于疯牛病可以感染多种猫科动物并且可以自然感染绵羊和山羊<sup>[74,75]</sup>,和患病动物的密切接触或食用被疯牛病感染的羊肉都可能引起疯牛病. 另外,目前在欧美国家进行的抗典型性羊瘙痒病培育羊仍然可以被非典型性羊瘙痒病毒感染<sup>[76~79]</sup>. 由于非典型性羊瘙痒病可以突破种间屏障<sup>[80]</sup>,因此有可能导致人的疯牛病. 同时,由于散发型克雅氏和遗传型克雅氏病等的存在,消灭人类朊病毒病成为不可能. 事实上,由于人的传染性海绵状脑病在大多数发展中国家和不发达国家目前仍然不能被准确鉴定,这些国家中存在医源性克雅氏病暴发的潜在可能性. 此外,鉴于无临床症状新变异型克雅氏病的存在,如由PRNP基因129甲硫氨酸/缬氨酸杂合子和129缬氨酸纯合子导致更长潜伏期的无临床症状克雅氏病,即使在发达国家仍然存在医源性克雅氏病传染的可能性. 特别值得注意的是,由于中国汉族人群对朊病毒病易感的PRNP基因129甲硫氨酸纯合子的比例高达98%<sup>[81]</sup>,新变异型克雅氏病对中国人群健康的潜在危害尤其值得关注.

除对动物和人类健康的影响外,朊病毒病的流行可能造成巨大的生态危机. 目前鹿慢性消耗病仍然在北美的野外传播并有扩大趋势<sup>[27]</sup>,而自然种群中患慢性消耗病的鹿更容易被美洲狮捕食并因此可能引起地方性食物网的失衡及生态系统营养循环的破坏<sup>[82,83]</sup>.

疾病从有效控制阶段到彻底消除无不经过数十年时间. 在此期间,疾病监测和流行病学调查不仅直接反映疾病的流行状况,而且是疾病消除的重要手段. 对于朊病毒,其生物学本质目前还有许多未解之谜,同时仍没有特异性预防和治疗手段,因此加强朊病毒病的监测和流行病学调查将促进人类对朊病毒病演化的理解并提出新的应对措施.

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Summary for “朊病毒疾病将如何发展?”

## How will prion disease evolve?

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Transmissible Spongiform Encephalopathy (TSE) or prion disease is caused by the infectious agent prion or scrapie prion protein (PrP<sup>Sc</sup>). In animals, prion disease includes scrapie in sheep and goat; mink spongiform encephalopathy in mink; chronic wasting disease in elk and deer, and bovine spongiform encephalopathy (BSE), a.k.a. mad cow disease in cattle. Human TSE includes, Kuru; Creutzfeldt-Jakob Disease (CJD); Gerstmann-Sträussler-Scheinker Disease (GSS) and more recently, variant CJD, which is thought to be caused by the transmission of BSE to human. The search for the transmissible agent of TSE went through many decades of uncertainty. In contrast to all other known pathogens, the TSE agent was shown to lack nucleic acids and appeared to co-purify with proteins. It was not until the 1980s that the infectious agent of TSE was shown to be a protein. Remarkably, the gene encoding for this protein is present in normal mammals. Subsequently, the word “prion”, an acronym for “proteinases infectious particle” was coined to explain this conundrum. It was postulated that the central event in the pathogenesis of prion diseases is the conversion of the normal cellular prion protein (PrP<sup>C</sup>) into an intermediate isoform (PrP<sup>\*</sup>) and finally the pathological, protease-resistant and infectious, PrP<sup>Sc</sup>. While the concept of “protein only hypothesis” is firmly established, the processes by which the conversion occurs, and the mechanisms by which PrP<sup>Sc</sup> causes pathogenesis remain incompletely understood. Furthermore, despite exhaustive investigations, the normal physiologic functions of PrP<sup>C</sup> remain elusive. It is clear, however, that expression of PrP<sup>C</sup> in the central nervous system (CNS) is required for the neurotoxicity of PrP<sup>Sc</sup> as *prnp* null mice do not develop neurodegeneration.

As a rare neurodegeneration disease, prion disease occurs with 1–3 cases in a million people per year, among which approximately 85% is sporadic without known agents, 10%–15% is genetic due to somatic mutations of the *PRNP* gene, and less than 1% is infectious. It is likely that the first occurrence of mad cow disease in England was caused by feeding meat and bone meal (MBM) contaminated by prions. How the first prion strain causing scrapie, chronic wasting disease, and transmissible mink encephalopathy remains obscure. For the past years, an international ban on MBM feeding has greatly reduced the occurrence of prion diseases, however, several reasons indicate that prion diseases will not be eradicated. First, somatic mutations of *PRNP* naturally occur, albeit at a rare frequency. Second, prions can adapt to new hosts, thus increasing their host range and overcoming the transmission barrier. Third, prions remaining in the field are infectious, and in some cases may become more infectious after binding to soil, as evidenced by the spread of chronic wasting disease among otherwise healthy deer populations. Fourth, samples from asymptomatic CJD patients or patients who are misdiagnosed under certain situations can contaminate medical instruments or be transplanted unintentionally, thus causing prion disease. More recently, it is postulated that the prion phenomenon, as defined by “the conversion of a normal protein to become an infectious protein” may also contribute to other neurodegenerative diseases. Hence, studying the pathogenesis of prion disease may provide novel insights into the underlying mechanisms of more common neurodegenerative diseases, such as Alzheimer’s disease and Parkinson’s diseases.

**prion disease, transmissible spongiform encephalopathy, mad cow disease, scrapie, PrP<sup>Sc</sup>, PrP<sup>C</sup>, protein conformational change**

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