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The Repeat Expansion Diseases: the dark side of DNA repair?

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Abstract

DNA repair normally protects the genome against mutations that threaten genome integrity and thus cell viability. However, growing evidence suggests that in the case of the Repeat Expansion Diseases, disorders that result from an increase in the size of a disease-specific microsatellite, the disease-causing mutation is actually the result of aberrant DNA repair. A variety of proteins from different DNA repair pathways have thus far been implicated in this process. This review will summarize recent findings from patients and from mouse models of these diseases that shed light on how these pathways may interact to cause repeat expansion.

Keywords

Repeat Expansion Diseases; Mismatch Repair; Base excision repair; transcription coupled repair; global genome repair; oxidative damage

1. Introduction

DNA damage repair is essential for human survival. However, it is becoming increasingly apparent that some repair processes act as double-edged swords, protecting the genome against some sorts of mutations whilst increasing the risk of others. The Repeat Expansion Diseases may represent one such example of a class of human genetic disorders that arise because of DNA repair gone wrong. These diseases comprise the 20+ human genetic conditions that arise from an increase (expansion) in the number of repeats in a particularly unstable tandem repeat array (Table 1). The disease-associated tandem repeats that have been identified thus far involve units of 3-12 bases. The consequences of the expansion depend on some combination of the location of the repeat within the affected gene, the size of the repeat unit, the number of repeats present in the allele and the sequence of the repeat (Discussed in [1] and chapters therein). The mechanism of expansion is unknown. However, as will be discussed below, growing evidence supports the idea that disease critical

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expansions result from the error-prone processing of these repeats by one or more DNA repair pathways that normally protect the genome against DNA damage.

The repeat instability in these disorders is likely to be very different from the generalized microsatellite instability (MSI) seen in many forms of cancer since MSI involves the gain or loss of a few repeat units (reviewed in [2]), while in the Repeat Expansion Diseases the repeat tract shows a strong expansion bias, in some cases adding hundreds, if not thousands of repeats in the space of a single generation. In addition, as will be discussed in more detail later, mutations that increase MSI actually decrease repeat expansion.

2. Disease associated repeats form unusual DNA structures

All of the disease-associated repeats form unusual secondary structures. Most repeats form intrastrand structures like hairpins/stem-loops, G-quadruplexes and *i*-motif tetraplexes, whilst others form intramolecular triplexesandor become unpaired under moderate superhelical stress (See [3-7] for recent reviews). Many of these structures contain single-stranded regions, mismatched bases or unusual hydrogen bonding interactions such as Hoogsteen and other non-Watson-Crick base pairs. In principle, these structures could form any time that the DNA is unpaired e.g., during DNA replication, repair or transcription and there is evidence that some of these structures do indeed form *in vivo* [8, 9]. Interruptions to the purity of the repeat are commonly seen in different diseases and these interruptions frequently reduce both the stability of these secondary structures (*e.g.*, [10, 11]) and the risk of expansion (*e.g.*, [12-15]). Current thinking is that these structures are somehow responsible for the tendency of the repeats to expand.

Many of the repeats also form persistent co-transcriptional RNA:DNA hybrids (or R-loops) [8, 16-19]. Bidirectional transcription through these repeats can result in the generation of double R-loops [20]. The single-stranded regions of the R-loops may themselves be prone to damage that could trigger expansions. They are also likely to increase the chances that secondary structures are formed by the unpaired DNA strand.

Work *in vitro*, in *E. coli*, yeast, flies and various tissue culture model systems has provided important clues as to the many ways that expansions can be generated in different contexts and there are a number of comprehensive reviews that summarize this work in some detail [3-7]. Our current thinking about how these repeats expand in the Repeat Expansion Diseases is informed by this work. However, because of space limitations this review will focus on what we have learnt from the natural history of the expansion process in affected humans and from different mouse and human disease-derived models. Furthermore, while expansions and contractions may represent different outcomes of the same underlying process, evidence suggests that genetic and environmental factors that affect expansions don't necessarily affect contractions the same way (*e.g.*, [21-23]). Thus, it may be that expansions and contractions involve different mechanisms. Given the limited space available, this review will focus on data that specifically addresses the expansion process.

3. Expansion in mammalian cells does not require chromosomal replication

In affected humans expansions are often seen in tissues with a low proliferative capacity including brain, liver and muscle (*e.g.*, [24-27]). Expansions have been observed in non-dividing cells in affected humans including neurons of patients with Huntington disease (HD) [28, 29], Dentatorubral–pallidoluysian atrophy (DRPLA) [30] and Friedreich ataxia (FRDA) [31]. Expansions are also seen in the oocytes of women with myotonic dystrophy type 1 (DM1) [32, 33] and a maternal age effect is seen on the transmission of expanded alleles in DM1, Fragile X syndrome (FXS) and FRDA [13, 34, 35]. Since neurons are post-mitotic and oocytes are suspended in dictyate arrest from late in fetal life, this would support the idea that expansion is independent of chromosomal replication. Furthermore, all mouse models for the Repeat Expansion Diseases studied to date also show expansions in tissues with a low proliferative capacity (*e.g.*, [22, 36-38]). Expansion is seen in terminally differentiated neurons in different mouse models of HD [29, 39] and paternally transmitted expansions have been shown to occur in post-meiotic haploid cells in a mouse model of HD [40]. In embryonic fibroblasts from a DM1 mouse model, chemical or genetic cell arrest of the cell cycle at a variety of stages did not block expansions and in some cases actually increased the expansion frequency [41].

Thus, while some expansions may arise from problems associated with chromosomal replication, data from affected humans and of mouse models of the Repeat Expansion Diseases demonstrate that expansions in disease-relevant cells like neurons and gametes involves a process that is independent of genome duplication. Since expansion mechanisms involving chromosomal replication have been thoroughly covered elsewhere [3-6], this review will focus on mechanisms that can occur in non-dividing cells.

4. Expansion is facilitated by transcription or by transcriptionally competent chromatin

While depletion of proteins that cause transcriptional silencing or treatment with small molecule inhibitors of such proteins do affect repeat expansion in different ways [42-45], the reported effect is not thought to be mediated by a change in the chromatin or transcriptional activity of the repeat-containing sequence [42, 45]. Nonetheless, there is evidence from a number of different systems suggesting that transcription through the repeat is important for expansion. For example, a clear requirement for transcription or at least transcriptionally competent chromatin can be seen in FXS one of the Fragile X-related disorders (FXDs). In this disorder the repeat is stabilized when the gene in which the repeat is located undergoes repeat-mediated gene silencing [46-49]. Furthermore, in a mouse model of the FXDs where the repeat falls below the threshold for repeat-mediated silencing, expansions in females only occur when the repeat is on the active X chromosome [50]. A re-examination of data from women who carry similar sized alleles [51] demonstrates that the same is true in humans.

However, there is not a simple relationship between the amount of transcription and the extent of expansion in either mice or humans (*e.g.*, [36, 37, 52]). It could be that expansion requires an open chromatin configuration rather than transcription *per se* or that

transcription is not rate limiting for expansion. It has also been suggested that the expansion frequency is related to the rate of transcription elongation rather than to the absolute levels of transcription [53]. This idea is based on a comparison of the repeat instability in the striatum and cerebellum of HD mouse models. While these two tissues show similar steady state levels of transcription, transcription elongation rates are higher in the striatum, which also shows higher levels of expansion [53]. However, the difference in the expansion rates of these tissues has also been correlated with differences in the levels of expression of some of the proteins involved in the expansion process [54, 55]. It remains to be seen whether either of these correlations hold up when additional tissues are analyzed.

5. A diverse collection of proteins involved in DNA repair are important for expansion

A number of different proteins have been implicated in repeat expansion (Table 2). These proteins include general DNA processing enzymes that are involved in a wide variety of different biological processesas well as proteins central to specific DNA repair and recombination pathways.

5.1. General DNA processing proteins

DNA ligase 1 (LIG1) is involved in sealing nicks generated during lagging strand DNA synthesis, as well as during DNA repair and recombination. A *Lig1* hypomorphic mutation had no effect on repeat expansion in the FXD mouse [21]. However, the same mutation reduced maternally transmitted expansions in an HD mouse [56]. This may reflect a maternal-specific expansion process. However, since heterozygosity for this allele had the effect as homozygosity for this allele, this result is difficult to interpret. It has been suggested to reflect a potential dominant negative effect of the hypomorphic allele [56]. However, given that a *Lig1* null mutation is embryonic lethal, it might be premature to exclude a more general role for this protein in repeat expansion.

There is also currently no genetic evidence for a role for Flap endonuclease 1 (FEN1) in repeat expansion in mammals. FEN1 often works upstream of LIG1 to generate the correct substrates for ligation in a variety of different DNA processing pathways. Despite the fact that work *in vitro* has shown that hairpins formed by some of the repeats block FEN1 processing [57], heterozygosity for a *Fen1* null mutation did not reduce expansions in DM1, HD or FXD mouse models [21, 58, 59]. However, absence of FEN1 is also embryonic lethal and since it is possible that *Fen1* heterozygous mice are not haplo insufficient, it is probably also too early to exclude a role for FEN1 in the expansion process.

5.2. Double-strand break repair (DSBR) proteins

Loss of RAD52, a protein involved in homologous recombination (HR), reduced the size of germ line but not somatic expansions in a mouse model of DM1 [60]. However, neither the loss of this protein nor the loss of RAD54, another HR protein, affected the expansion frequency [60]. Furthermore, expansions are seen in haploid sperm of HD mice in which there is no sister chromosome or sister chromatid with which to recombine [40]. Thus an HR-based mechanism for expansion is unlikely. However, since RAD52 also cooperates

with 8-oxoguanine DNA glycosylase (OGG1) in the repair of oxidative lesions via base excision repair (BER) [61], this protein may affect the expansion size independent of its role in DSBR. The absence of DNA-dependent protein kinase (DNA-PK), a protein involved in non-homologous end joining (NHEJ), had no effect on the expansion frequency in this model [60].

5.3. Mismatch Repair (MMR) proteins

While the loss of MMR proteins increases MSI, the opposite is true in mouse and human cell models of repeat expansion where some of these proteins are actually required for expansion to occur. MutSα, a heterodimer of the MutS homolog 2 (MSH2) and the MutS homolog 6 (MSH6), and MutSβ, a heterodimer of MSH2 and the MutS homolog 3 (MSH3), are the complexes responsible for lesion recognition in the MMR pathway [62]. The substrates with which they interact are partially overlapping, with MutSα recognizing single base mismatches and small insertions and deletions (INDELs), and MutSβ recognizing larger INDELs. While there is some variability between different mouse models (*e.g.*, [63, 64]), a case can be made for MutSβ being required for expansions in most mouse models [22, 45, 65-68]. However, MSH6, and thus MutSα has been suggested to promote somatic expansions in an FRDA mouse model [69]. The effect of knockdown of MSH6 in induced pluripotent stem cells derived from FRDA patients [70] and overexpression of MutSβ in a human tissue culture model [71] also supports a role for these complexes in generating expansions in humans.

The requirement for MMR proteins extends to complexes that act downstream of MutS in the MMR pathway such as MutLα, a heterodimer of MutL homolog 1 (MLH1) and postmeiotic segregation increased 2 (PMS2), and MutLγ, a heterodimer of MLH1 and the MutL homolog 3 (MLH3) protein. MutLα has been implicated in at least 50% of somatic expansions in a DM1 mouse model [72] but seems to be excluded from a role in expansion in the FRDA mouse [69]. MutLγ is required for all somatic expansions in an HD mouse model [73] and perhaps, by inference, in a FRDA mouse model as well [69, 74]. The importance of MutLγ is consistent with the observation that MutSβ is required for expansion in most mouse models and the fact that MutLγ is thought to interact with MutSβ but not MutSα [75].

While it was once thought that MMR was confined to S phase, recent work *in vitro* has shown that extrahelical CAG-repeats can activate the latent endonuclease activity of MutLα. This activation occurs in the absence of the strand discontinuities that arise during genomic replication that normally serve this purpose [76]. This activation allows loading of proliferating cell nuclear antigen (PCNA) thus enabling successful MMR to occur outside of S phase. However, whether other repeats are able to activate MutLα or whether the repeats are able to activate MutLγ is unknown.

While the requirement for MutS and MutL proteins makes a strong case for an MMR-based mechanism, work in Cynthia McMurray's laboratory has shown that binding of MutSβ to the CAG-hairpin changes the properties of mismatch recognition [77]. While this result has been challenged [78], the McMurray group have gone on to show using single-molecule fluorescence resonance energy transfer (smFRET) that a subset of the hairpins form a unique

DNA junction that traps MutSβ on the template [79]. It has been suggested that this prevents classical MMR and may divert the hairpin substrate into another DNA repair pathway that ultimately gives rise to expansions. Expansion in an *in vitro* model system can be seen even in the absence of MMR proteins [80, 81]. Furthermore, in a HeLa nuclear extract, excess MutSβ does not inhibit or promote CTG or CAG repair of preformed hairpin substrates [78, 82]. This would be consistent with the idea that MutSβ promotes a process such as the formation of secondary structures rather than determining repair outcome.

5.4. Base Excision Repair (BER) proteins

Loss of the DNA glycosylases OGG1 and nei endonuclease VIII-like 1 (NEIL1) reduces somatic expansions in a mouse model of HD [83, 84]. OGG1 and NEIL1 are involved in BER, the major pathway by which oxidative damage is repaired in mammals. Both enzymes are involved in the removal of oxidized bases from DNA, one of the first steps in the BER pathway. A more general role of oxidative damage repair in generating expansions is suggested by the observation that potassium bromate ($KBrO_3$), a potent DNA oxidizing agent, increases germ line expansions in a mouse model of the FXDs [21]. The loss of NEIL1 in the HD mouse model also reduces the average size of expansions seen on intergenerational transmission although it does not affect the absolute germline expansion frequency [84]. The fact that neither OGG1 nor NEIL1 reduce germ line expansion frequencies may reflect the contribution of other DNA glycosylases to the expansion process. However, mutations in alkyladenine glycosylase (AAG), a DNA glycosylase that excises a variety of alkylated bases, or homologue of *Escherichia coli* endonuclease III (NTH1), which prefers to excise thymine glycol, did not reduce expansions in the HD mouse model [83]. The action of DNA glycosylases results in the generation of an a basic site that is the substrate for the apurinic/apyrimidinic endonuclease 1 (APE1). The nicks generated by APE1 are then channeled into either the single nucleotide (SN) or short patch (SP) BER pathway or the long patch (LP) BER pathway. It is possible that BER-mediated expansion could be initiated in response to other sources of a basic sites or nicks. One potential source of such a basic sites is depurination which is thought to be very common in GC-rich regions [85]. Such sites can be processed by APE1 to generate a nick upon which the BER process can act. However, at this time there is no data implicating proteins that act downstream of the generation of a basic sites in the repeat expansion process in any model or tissue culture model.

5.5. Nucleotide Excision Repair (NER) proteins

Proteins involved in NER also affect repeat expansion. Two overlapping NER pathways operate in mammalian cells, Global Genome Repair (GGR) and Transcription Coupled Repair (TCR) (reviewed in [86]). The TCR pathway is confined to the repair of transcription blocking lesions on the transcribed strand of active genes, while GGR occurs genome wide. The GGR and TCR pathways converge downstream of the DNA damage recognition step.

The only NER protein specific for GGR that has been examined in mice is xeroderma pigmentosum, complementation group C (XPC), the earliest DNA damage detector in the initiation of GGR. Loss of XPC did not affect striatal expansions or germ line expansions in a mouse model of HD [64]. However, loss of the xeroderma pigmentosum, complementation

group A (XPA) protein that acts in both GGR and TCR does affect repeat expansion in a mouse model of SCA1 [88]. Loss of XPA did not affect the intergenerational expansion frequency or the extent of somatic expansion in liver and kidney, but it did dramatically reduce the expansions seen in striatum, hippocampus and cerebral cortex [88]. Although expansions were dramatically reduced, they were not eliminated completely even in neural tissue suggesting that XPA may be playing an auxiliary role in expansion outside of NER. For example, XPA is known to bind with higher affinity to DNA junctions than to DNA damage [89]. XPA may thus help stabilize the secondary structures thought to be the substrates for expansion. While the different effects of the loss of XPA in different tissues could suggest the existence of tissue-specific expansion mechanisms, it is also possible that in some tissues the core factors necessary for expansions are present in sufficient quantities such that auxiliary proteins are not needed.

Cockayne Syndrome B (CSB), a transcription elongation factor that is essential for early steps in TCR, promotes both germ line and somatic expansions in the FXD mouse [90]. However, CSB is not essential for expansions either since its loss does not eliminate them all. Thus CSB is also likely acting as an accessory factor to promote expansions in a pathway other than TCR. It might facilitate expansion via a BER-based mechanism since CSB is known to up-regulate OGG1 expression [91] and to promote the incision activities of OGG1, NEIL1 [92, 93] and APE1 [94]. It could also act via its ability to modify chromatin and/or increase transcription elongation [95, 96]. While very few genetic modifiers of expansion risk in humans have thus far been identified, it is interesting to note that single nucleotide polymorphisms (SNPs) in three TCR-related genes are associated with an increased expansion risk in Machado-Joseph Disease (MJD/SCA3) alleles, including one in the ERCC6/CSB gene [97].

6. An integrated model for repeat expansion

Thus, while DSBR does not seem to be involved in repeat expansion in mammalian systems, proteins from a variety of other DNA repair pathways have been shown to contribute significantly to expansion. Given the different contributions of some of these proteins in different disease models, in males and females and in different cell types, it is possible that more than one expansion mechanism is responsible. However, since expansions have a number of unique features and share a common dependence on MMR factors, it could be argued that a single mechanism is at work. Most of the reported differences between disease models, tissue and genders could be related to the effects of different genetic backgrounds, the differential expression of the proteins involved and/or the variable contribution of proteins that promote but are not essential for expansion. Furthermore, although the proteins implicated in repeat expansion act in a wide variety of different DNA repair pathways, it is becoming increasingly apparent that there is a lot of cross talk between these pathways (e.g., [98, 99]).

Thus, it may be possible to reconcile all of the data described above into a single model. Such a model would have to accommodate the fact that expansions can occur independent of genomic replication via a process in which transcription or an open chromatin configuration is important. It should also account for the strong expansion bias that is seen in the Repeat

Expansion Diseases. It would also have to accommodate the contribution of MMR proteins and the involvement of proteins more typically associated with BER and TCR. The requirement for transcriptionally competent chromatin may simply reflect the fact that transcription through the repeat creates the opportunity for the secondary structures that are thought to be the expansion substrates to form. However, it is also possible that it reflects a DNA repair process other than TCR that is also confined to actively transcribed regions of the genome. Models for repeat expansion that involve LP BER are thus appealing since recent work suggests this process occurs preferentially in actively transcribed regions of the genome [100, 101].

The role of DNA glycosylases normally involved in the initiation of BER in response to oxidative stress suggests that an early step in the expansion process may be the recognition and removal of damaged bases in DNA and the generation of nicks as illustrated in Fig. 1. It has been suggested that LP BER is the major BER pathway for the repair of 8-oxoG lesions and AP sites [102]. LP BER occurs via one of two sub-pathways. Both sub-pathways involve Polβ, the polymerase responsible for SP BER. One sub-pathway also involves Polδ/Polε, two processive polymerases with stronger strand displacement activities than Polβ. This generally results in the synthesis of 2-13 nucleotides [103]. The second sub-pathway involves Polβ acting without Polδ or Polε to carry out a more limited gap-filling reaction that involves the synthesis of fewer nucleotides [104]. There is *in vitro* data to support the idea that expansions could arise in the Polβ/Polδ/Polε-dependent pathway if strand-slippage occurred on the nascent strand, an event that would be facilitated by secondary structure formation, and if priming by Polβ then occurred from the slipped position [105]. Expansions may also arise by structure formation on the displaced strand that prevents proper flap processing. Expansions could arise even via the Polδ/Polε-independent sub-pathway if some Polβ-mediated strand displacement occurs that results in the formation of a secondary structure that is not properly processed by FEN1 as illustrated in the bottom right hand side of Fig. 1. A form of alternate FEN1 cleavage has been suggested to facilitate this process [106]. A role for both sub-pathways may help explain the different “jump sizes” are seen in different organs of mouse models (e.g., [36, 83, 107]). For example, expansion in organs showing large “jumps” could occur via the use of the first pathway while small “jumps” occur via the use of the second. The choice of which pathway is used may depend on the relative levels of Polβ, Polδ and/or Polε. Models in which expansions result from the failure to properly process 5’ flaps generated by strand-displacement synthesis are appealing since they could account for the strong expansion bias observed in many Repeat Expansion Diseases.

CSB may contribute to the generation of nicks via its ability to enhance the activity of DNA glycosylases and APE1, while RAD52 may also act at this step to enhance OGG1 incision. The effect of CSB and RAD52 may only be apparent in cells in which the incision process is somehow limiting. MMR proteins may increase the likelihood that oxidative damage will occur by stabilizing secondary structures that are sensitive to such damage [108]. XPA may act in an auxiliary capacity to facilitate expansion by contributing to this stabilization since MutSβ generates a strong bend when it binds to an INDEL [109] and XPA binds preferentially to bent DNA [87]. The effect of XPA may only be apparent in neural cells if

MutSβ is limiting there but not in other cells. Alternatively another protein may substitute for XPA outside the central nervous system (CNS). MMR proteins may also act later in the LP BER pathway by stabilizing the hairpins generated by strand-slippage thus increasing the likelihood that priming will occur from the slipped position during repair synthesis. They may also reduce the likelihood that FEN1 would be able to properly process any flaps generated by strand-displacement during LP BER.

However, the fact that MutL complexes that act downstream of MutSβ/MutSα in the MMR pathway are important for expansions suggests that the role of MMR proteins may extend beyond simply stabilizing the substrates for expansion. Thus it is possible that MMR can use the nicks generated during early steps of BER to load EXO1 and other proteins required for MMR as illustrated in Fig. 1(b).

Perhaps the most intriguing finding in the field in recent months is that there is a specific requirement for MutLγ rather than MutLα for expansion in some mouse models. This is of interest since MutLγ is present only in very low levels in mammalian cells and while it colocalizes with sites of DNA damage, it has been suggested that it does not contribute significantly to normal MMR in mammals [110]. The role of MutLγ is thus enigmatic and a better understanding of the pathways in which it acts is essential to our understanding of the expansion mechanism.

Note added in Proof

We have recently demonstrated that heterozygosity for a hypomorphic PolB mutation reduces the expansion frequency in a FXD mouse model (Lokanga, Senejani, Sweasy and Usdin. Heterozygosity for a hypomorphic PolB mutation reduces the expansion frequency in a mouse model of the Fragile X-related disorders. PLoS Genetics. 11, 2015, e1005181). It also results in a preferential loss of smaller expansions. These data lend support to the model shown in Fig. 1.

Acknowledgments

In a review of a subject as broad as this one, it is difficult to cite all of the relevant literature. We have thus tried to provide illustrative examples rather than generating an exhaustive citation list. We apologize to those whose contributions to the field, for reasons of space, were not acknowledged specifically.

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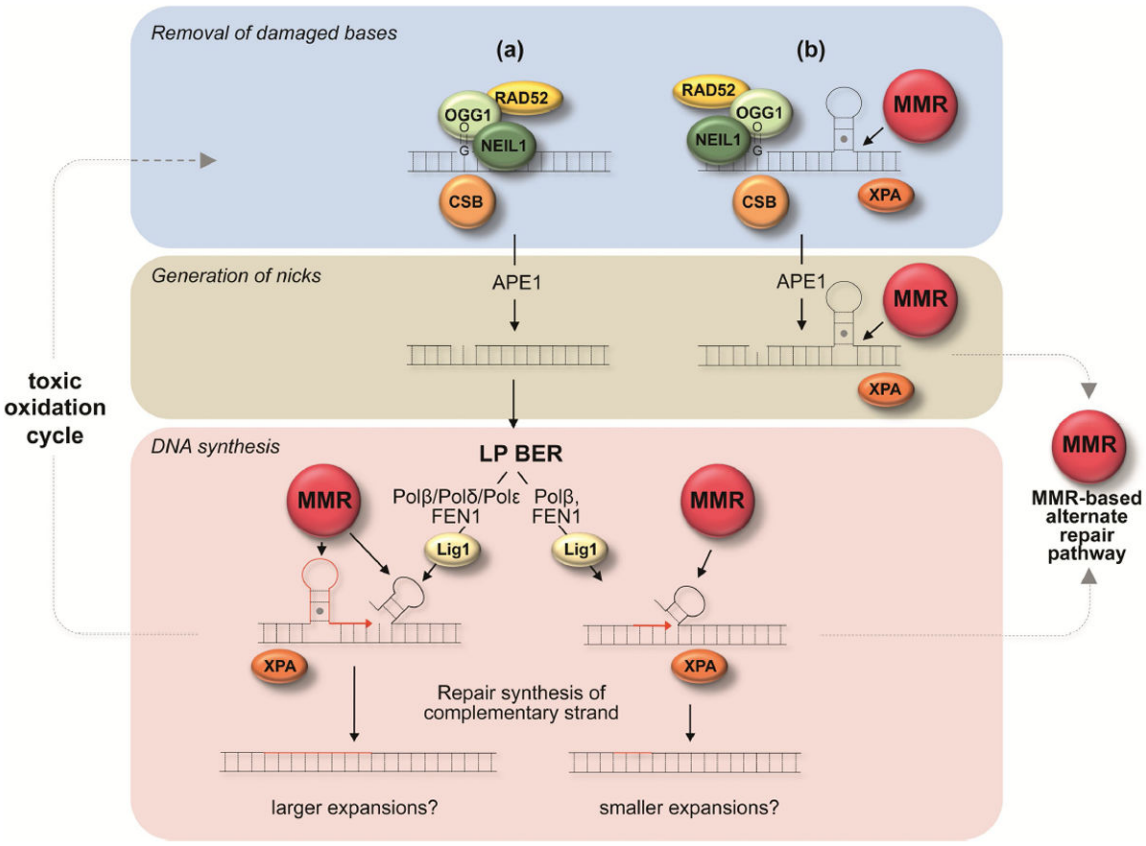

Fig. 1. An integrated model for the repeat expansion mechanism in mammals

Proteins directly implicated in generating expansions in mouse models or human cells are shown as colored spheres. MMR refers to a complex consisting of the MMR proteins MutSα or MutSβ together with either MutLα or MutLγ. Red strands represent newly synthesized DNA. The repair of DNA damage within the repeat is initiated by DNA glycosylases in response to oxidized bases. This is followed by the removal of the abasic site by APE1 to generate a nick. (a) Repair of the nick may proceed via an LP BER pathway that involves Polβ, Polδ and perhaps Polε [111]. Strand-slippage/hairpin formation at the 3' terminus of the nascent strand arising during strand displacement synthesis by Polδ/Polε could result in expansion if the hairpin is not removed because Polβ synthesis prevents proof-reading by Polδ/Polε [105]. Formation of a secondary structure on a displaced flap could also result in expansion if proper processing were blocked. A second LP BER pathway that involves Polβ but not Polδ/Polε may generate small expansions by stepwise and distributive gap-filling by Polβ and single-nucleotide gap formation by FEN1 [106]. Improper coordination between Polβ and FEN1 could lead to a small amount of strand displacement with the formation of a small hairpin in the displaced flap. FEN1 "alternate cleavage" of a short 5' flap at the base of the hairpin could produce a ligatable nick that after ligation results in incorporation of hairpin bases into the "repaired" strand.(b) Alternatively, a nick close to a repeat loop-out formed during transcription or replication may allow loading of MutSβ/MutSα complexes and the diversion of the normal BER process to produce an MMR-dependent expansion. MMR proteins may also act in the LP BER-based expansion processes shown in (a) to

stabilize secondary structures formed by the repeats and perhaps to prevent their removal by enzymes like FEN1. XPA, CSB and RAD52 may act in an auxiliary capacity in either of these pathways via the ability to stabilize secondary structures in the case of XPA, to facilitate incision by OGG1 in the case of RAD52 [61] and to increase incision or to facilitate the formation of an optimal chromatin or transcriptional state in the case of CSB (reviewed in [112]). Loops generated at any stage of the expansion process are susceptible to oxidative damage that could produce result in repeated “toxic oxidation cycles” that could result in multiple rounds of BER-mediated expansions [108].

Table1

Repeat unit[1]	Disease[2]	Gene	Repeat location	Normal repeat length	Pathogenic repeat length	Refs
CAG	Dentatorubral–pallidoluysian atrophy (DRPLA)	*ATN1*	exon	7-35	49-93	[113, 114]
	Huntington disease (HD)	*HTT*	exon	9-35	36-121	[115, 116]
	Spinal and bulbar muscular atrophy (SBMA)	*AR*	exon	9-34	38-62	[117]
	Spinocerebellar ataxia 1 (SCA1)	*ATXN1*	exon	6-42	39-83	[118]
	Spinocerebellar ataxia 2 (SCA2)	*ATXN2*	exon	14-31	32-200	[119, 120]
	Spinocerebellar ataxia 3 (SCA3)	*ATXN3*	exon	12-44	52-86	[121, 122]
	Spinocerebellar ataxia 6 (SCA6)	*CACNA1A*	exon	4-18	21-33	[123, 124]
	Spinocerebellar ataxia 7 (SCA7)	*ATXN7*	exon	4-35	37-306	[125]
	Spinocerebellar ataxia 12 (SCA12)	*PPP2R2B*	5' UTR	7-28	55-78	[126, 127]
	Spinocerebellar ataxia 17 (SCA17)	*TBP*	exon	25-42	45-66	[128-130]
CTG	Fuchs endothelial corneal dystrophy (FECD)	*TCF4*	intron	10-37	>50	[131]
	Huntington disease-like 2 (HDL2)	*JPH3*	3' UTR	6-28	40-59	[132, 133]
	Myotonic dystrophy 1 (DM1)	*DMPK*	3' UTR	5-38	>50	[134-137]
	Spinocerebellar ataxia 8 (SCA8)	*ATXN8*	3' UTR	15-37	>74	[138-140]
CGG	FRA7A[3]	*ZNF713*	intron	5-22	68, 72, ~450	[141]
	Fragile X–associated primary ovarian insufficiency (FXPOI)[4]	*FMR1*	5' UTR	<55	55-200	[142, 143]
	Fragile X–associated tremor/ataxia syndrome (FXTAS)[4]	*FMR1*	5' UTR	<55	55-200	[144]
	Fragile X syndrome (FXS)[4]	*FMR1*	5' UTR	<55	>200	[47, 145]
GCC	Fragile XE mental retardation syndrome (FRAXE MR)	*AFF/FMR2*	5' UTR	6-25	>200	[146, 147]
GAA	Friedreich ataxia (FRDA)	*FXN*	intron	8-33	>90	[148]
CCTG	Myotonic dystrophy type 2 (DM2)	*ZFN9*	intron	<30	75-11000	[149-151]
ATTCT	Spinocerebellar ataxia 10 (SCA10)	*ATXN10*	intron	9-32	800-4500	[152, 153]
G_2C_2TG	Spinocerebellar ataxia 36 (SCA36)	*NOP56*	intron	3-8	1500-2500	[154, 155]
G_4CC	Amyotrophic lateral sclerosis/Frontotemporal dementia (ALS/FTD)	*C9orf72*	intron	2-22	700-1600	[156, 157]
C_4GC_4GCG	Progressive Myoclonus Epilepsy (EPM1)	*CSTB*	promoter	2–3	30–78	[158, 159]

[1] The disorders are organized based on the sequence of the repeat unit in the coding sequence of the affected gene and on its location within that gene. However, in some cases an antisense transcript is produced that may contribute to disease pathology. In addition, Repeat-associated Non-ATG (RAN) translation can occur in some of these genes. Thus while the repeat may nominally be a non-coding region of the affected gene, pathology may nevertheless arise from the production of a toxic polypeptide.

[2] This table does not include a disorders like SCA31 that result from the "insertion" of a complex microsatellite [160]and the 9+ disorders that resultfrom the presence of a frequently interrupted and often stable microsatellite that encodes a polyalanine tract [161].

[3] A firm link has yet to be established between the repeat expansion mutation and symptoms of autism spectrum disorder reported in 2 families [141].

[4] These three diseases are all members of the Fragile X-related or *FMR1*-related disorders. Alleles with 55-200 repeats are referred to as Premutation (PM) alleles while alleles with >200 repeats are referred to as Full mutation (FM) alleles.

Table 2

DNA repair proteins directly implicated in repeat expansion

Protein	Model system	Cells affected	References
General factors			
LIG1	HD mouse	maternal germ line	[56]
MMR proteins			
MSH2	DM1, FXD and HD mice; tissue culture model of CTG/CAG and GAA/TTC-repeats	germ line and somatic cells	[22, 40, 45, 60, 66, 71, 162]
MSH3	DM1and HD mice, tissue culture model of CTG/CAG and GAA/TTC-repeats	germ line and somatic cells	[45, 65, 67, 68, 71, 163]
MSH6	FRDA mouse; FRDA iPSCs	somatic cells, iPSCs	[69, 70]
MLH1	HD and FRDA mice	germ line* and somatic cells**	[73, 74]
PMS2	DM1 mouse	somatic cells**	[72]
MLH3	HD mouse	somatic cells**	[73]
BER proteins			
OGG1	HD mouse	somatic cells	[164]
NEIL1	HD mouse	somatic cells	[84]
NER proteins			
CSB	FXD mouse	maternal germ line, some somatic cells	[90]
XPA	SCA1 mouse	neural cells	[88]
Recombination proteins			
RAD52	DM1 mouse	germ line	[60]

* in the FRDA mouse model loss of one *Mlh1* allele led to significant decrease in germ line expansions

** homozygous null mice are sterile so the effect of this mutation on germ line expansion was not examined in either the HD or the DM1 mouse models.