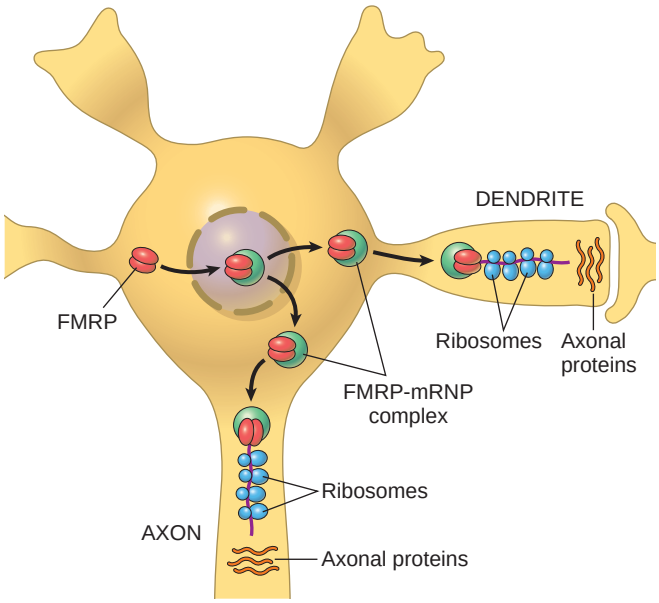

Figure 5-26 A model for the action of familial mental retardation protein (FMRP) in neurons. (Adapted from Hin P, Warren ST: New insights into fragile X syndrome: from molecules to neurobehavior. Trends Biochem Sci 28:152, 2003.)

occurs both in the perinuclear cytoplasm and in dendritic spines. Newly made FMRP translocates to the nucleus, where it assembles into a complex containing specific mRNA transcripts. The FRMP-mRNA complexes are then exported to the cytoplasm, from where they are trafficked to dendrites near neuronal synapses (Fig. 5-26). As would be anticipated, only mRNAs encoding proteins that regulate synaptic function are subject to shuttling by FMRP.

- *FRMP is a translation regulator.* At synaptic junctions FMRP suppresses protein synthesis from the bound mRNAs in response to signaling through group I metabotropic glutamate receptors (mGlu-R). Thus a reduction in FMRP in the fragile X syndrome results in increased translation of the bound mRNAs at the synaptic junctions. Such imbalance in turn causes permanent changes in synaptic activity and ultimately mental retardation.

Although demonstration of an abnormal karyotype led to the identification of this disorder, PCR-based detection of the repeats is now the method of choice for diagnosis.

Fragile X Tremor/Ataxia. **Although initially assumed to be innocuous, CGG premutations in the *FMR1* gene can cause a disease that is phenotypically different from fragile X syndrome through a distinct mechanism involving a toxic "gain-of-function".** A decade after the discovery that CGG repeat expansions cause fragile X syndrome, it became clear that approximately 20% of females carrying the premutation (carrier females) have premature ovarian failure (before the age of 40 years), and more than 50% of premutation-carrying males (transmitting males) exhibit a progressive neurodegenerative syndrome starting in their sixth decade. This syndrome, referred to as *fragile X tremor/ataxia,* is characterized by intention tremors and cerebellar ataxia and may progress to parkinsonism.

How do premutations cause disease? In these patients, the *FMR1* gene instead of being methylated and silenced continues to be transcribed. CGG-containing *FMR1* mRNAs so formed are "toxic." They accumulate in the nucleus and form intranuclear inclusions. In this process the aggregated mRNA recruits RNA-binding proteins. Perhaps sequestration of these proteins at abnormal locations leads to events that are toxic to the cell. In recent years, abnormal RNAs with toxic gain of function as a mechanism of tissue injury have also been implicated in certain myotoic muscular dystrophies.

KEY CONCEPTS

Fragile X Syndrome

- Pathologic amplification of trinucleotide repeats causes loss-of-function (fragile X syndrome) or gain-of-function mutations (Huntington disease). Most such mutations produce neurodegenerative disorders.
- Fragile X syndrome results from loss of FMR1 gene function and is characterized by mental retardation, macroorchidism, and abnormal facial features.
- In the normal population, there are about 29–55 CGG repeats in the *FMR1* gene. The genomes of carrier males and females contain premutations with 55 to 200 CGG repeats that can expand to 4000 repeats (full mutations) during oogenesis. When full mutations are transmitted to progeny, fragile X syndrome occurs.
- Fragile X tremor/ataxia due to expression of a *FMR1* gene bearing a premutation develops in some males and females. The accumulation of corresponding mRNA in the nucleus binds and sequesters certain proteins that are essential for normal neuronal functions.

Mutations in Mitochondrial Genes—Leber Hereditary Optic Neuropathy

The vast majority of genes are located on chromosomes in the cell nucleus and are inherited in classical Mendelian fashion. There exist several mitochondrial genes, however, that are inherited in quite a different manner. *A feature unique to mtDNA is maternal inheritance.* This peculiarity exists because ova contain numerous mitochondria within their abundant cytoplasm, whereas spermatozoa contain few, if any. Hence, the mtDNA complement of the zygote is derived entirely from the ovum. Thus, mothers transmit mtDNA to all their offspring, male and female; however, daughters but not sons transmit the DNA further to their progeny (Fig. 5-27). Several other features apply to mitochondrial inheritance. They are as follows:

- Human mtDNA contains 37 genes, of which 22 are transcribed into transfer RNAs and two into ribosomal RNAs. The remaining 13 genes encode subunits of the respiratory chain enzymes. Because mtDNA encodes enzymes involved in oxidative phosphorylation, mutations affecting these genes exert their deleterious effects primarily on the organs most dependent on oxidative phosphorylation such as the central nervous system, skeletal muscle, cardiac muscle, liver, and kidneys.