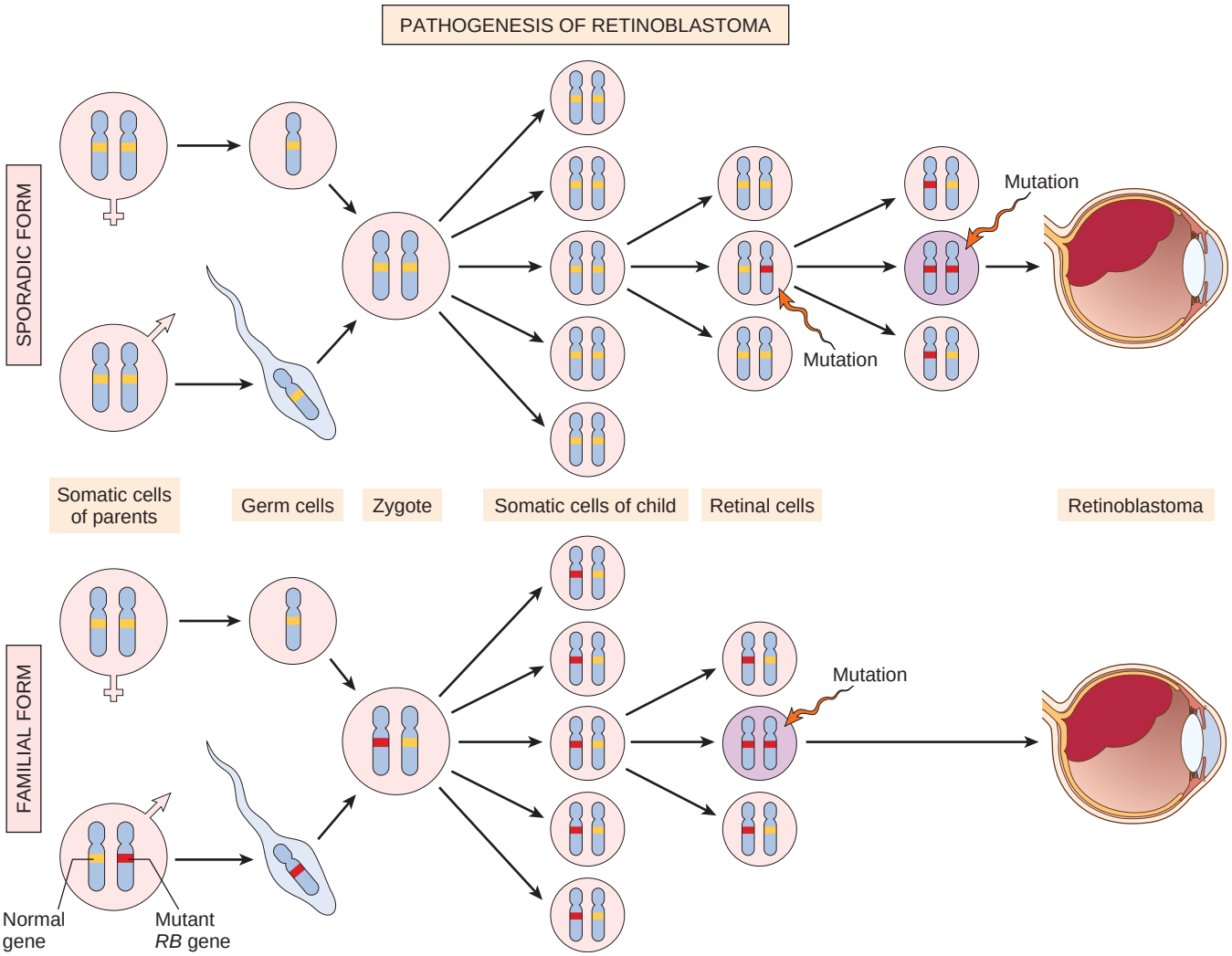

Figure 7-28 Pathogenesis of retinoblastoma. Two mutations of the *RB* locus on chromosome 13q14 lead to neoplastic proliferation of the retinal cells. In the sporadic form, both *RB* mutations in the tumor-founding retinal cell are acquired. In the familial form, all somatic cells inherit one mutated copy of *RB* gene from a carrier parent, and as a result only one additional *RB* mutation in a retinal cell is required for complete loss of RB function.

functions are listed in Table 7-7. Note that while tumor suppressors were initially thought of narrowly as proteins that put the brakes on cell cycle progression and DNA replication, it is now appreciated that some tumor suppressors prevent cellular transformation through other mechanisms, such as by altering cell metabolism (e.g., the serine-threonine kinase STK11, discussed later) or by ensuring genomic stability (e.g., the DNA repair factors BRCA1 and BRCA2). Thus, while most tumor suppressors have inhibitory effects on cell growth through one mechanism or another, a more inclusive definition of a tumor suppressor is simply a protein or gene that is associated with suppression of any of the various hallmarks of cancer.

We next consider consider how the major tumor suppressors function, focusing on those that are most frequently mutated in cancer or that highlight pathogenically important molecular mechanisms.

RB: Governor of Proliferation. **RB, a key negative regulator of the G_1/S cell cycle transition, is directly or indirectly inactivated in most human cancers.** RB also controls cellular differentiation. It exists in an active hypophosphorylated state in quiescent cells and an inactive hyperphosphorylated state in cells passing through the G_1/S cell cycle transition (Chapter 1). RB function may be compromised in two different ways:

- Loss-of-function mutations involving both *RB* alleles
- A shift from the active hypophosphorylated state to the inactive hyperphosphorylated state by gain-of-function mutations that upregulate CDK/cyclin D activity or by loss-of-function mutations that abrogate the activity of CDK inhibitors

As discussed previously, the decision of a cell to progress from G_1 into S is of great importance, since once a cell enters the S phase it is obligated to complete mitosis. High levels of CDK4/cyclin D, CDK6/cyclin D, and CDK2/cyclin E complexes lead to hyperphosphorylation and inhibition of RB, releasing E2F transcription factors that drive the expression of genes that are needed for progression to S phase (Fig. 7-29). Growth factor signaling pathways generally upregulate the activity of CDK/cyclin complexes