7.1 WINGLESS/β-CATENIN SIGNALING

Signaling by the Wnt family of secreted glycolipoproteins via the transcription co-activator β-catenin controls embryonic development and adult homeostasis. It was recognized for its function in embryonic development when genetic mutations produced abnormal fruit fly embryos. Later research found that the genes responsible for these abnormalities also influenced breast cancer development in mice. The clinical importance of this pathway has been demonstrated by mutations that lead to a variety of diseases, including breast and prostate cancer and glioblastoma. Because Wingless/β-catenin (Wnt/β-Cat) signaling is a key feature of epithelial cancers and seems to be critical for metastasis and EMTs, its specific modulation may help to eliminate drug-resistant cancer stem cells.[114]

All Wnt signaling pathways are activated by the binding of a Wnt protein ligand to a receptor belonging to the Frizzled family (FRZ), which passes the biological signal to the disheveled protein (DSH) inside the cell. In the *on* state, Wnt is associated with membrane-bound FRZ receptors and low-density lipoprotein receptor-related protein 5/6 (LRP5/6), leading to sequestration of the β-catenin phosphorylation complex, which is composed of DSH proteins, adenomatous polyposis coli (APC), axin, and GSK-3β. Consequently, phosphorylation of β-Cat is suppressed, and the free β-Cat escapes from the degradation and translocates from the cytoplasm to the nucleus, where it binds to the TCF/LEF (tumor cell factor/lymphoid enhancer factor) with the participation of a coactivator called CBP, activating the transcription of several target genes such as cyclin D1, c-myc, c-Jun, and fibronectin (Figure 11.26a). In the *off* state, the Dickkopf-1 (DKK1) protein, which is especially expressed in

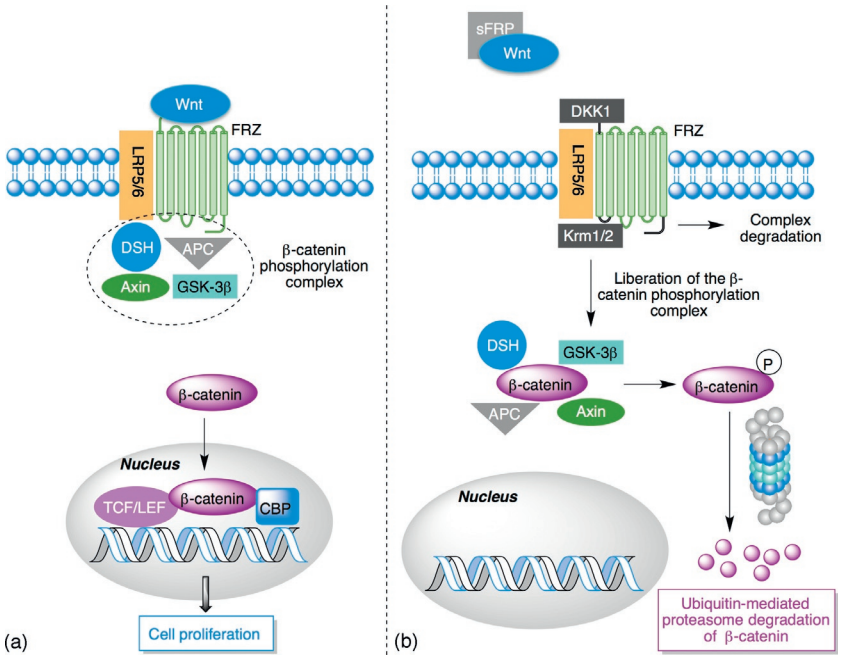

FIGURE 11.26

Processes taking place in the Wnt signaling pathway: (a) *on* state; (b) *off* state.