

7.2 INHIBITORS OF THE NOTCH SIGNALING PATHWAY

The Notch signaling pathway plays a critical role in cell fate, tissue patterning, and morphogenesis, as well as in the maintenance of the stem cells in glioblastoma, breast cancer, and some other tumors. The Notch1 receptor is a transcriptional activator of multiple genes, and its upregulation facilitates the activation of a number of signals leading to apoptosis inhibition and proliferation activation (Figure 11.28). This pathway has been correlated with increased tumor cell growth and survival.^{121,122}

Notch inhibition can be achieved at different levels. First, inhibitors of the SERCA (sarco/endoplasmic reticulum calcium ATPase) channels have been identified as indirect Notch1 inhibitors because the early maturation of Notch1 in the endoplasmic reticulum, in which the receptor is processed by proteases, requires SERCA-mediated Ca²⁺ influx for their proper folding.¹²³ The best-known SERCA inhibitors are thapsigargin, a toxin isolated from *Thapsia garganica*, and its analog 12-ADT that is contained in the prodrug G-202 specifically activated in prostate cancer cells (see Chapter 13, Section 2.1).

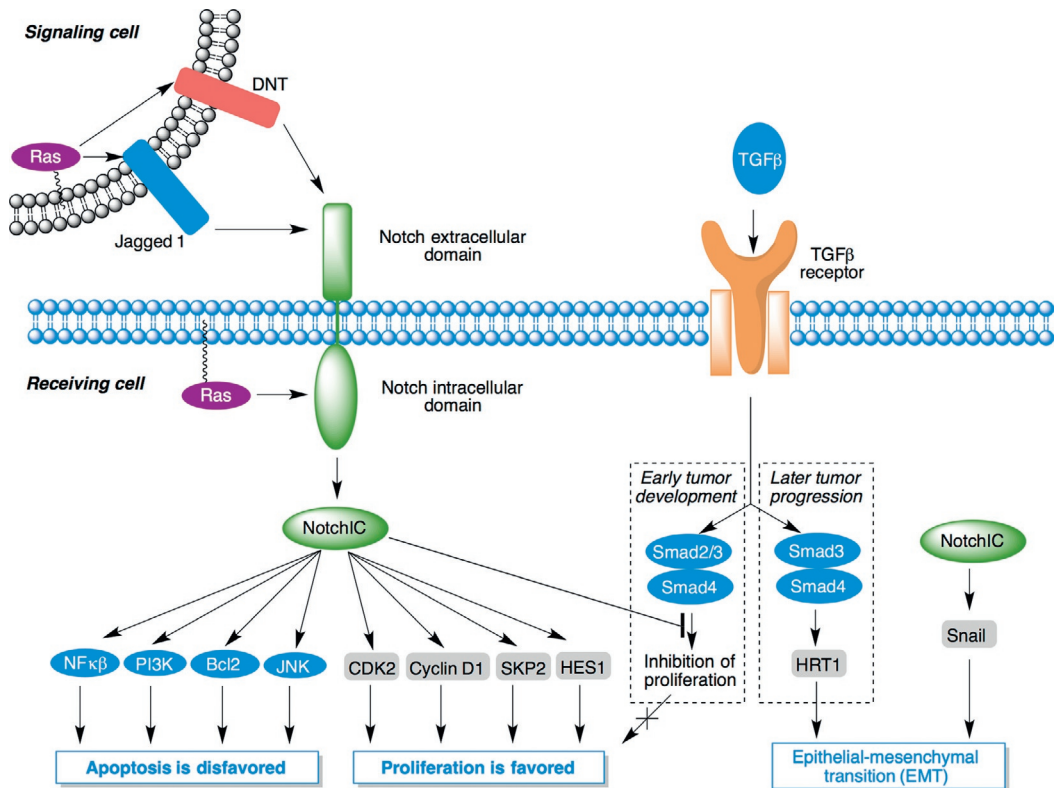


FIGURE 11.28

The Notch signaling pathway.