

Cell Cycle Regulation by TGF- β and hormones through the ubiquitin proteasome system

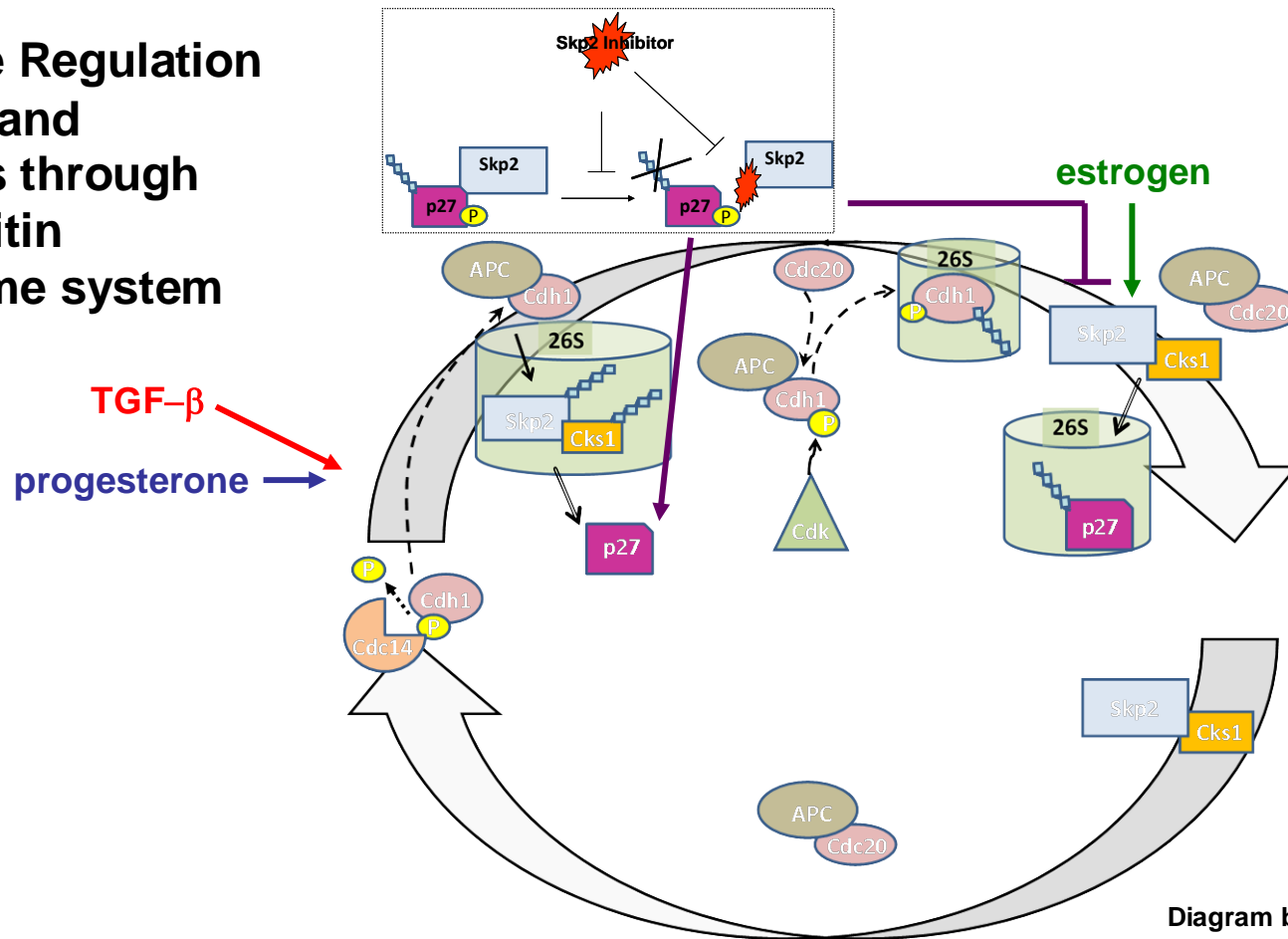


Diagram by Savvas Pavlides, PhD

The diagram depicts the growth regulatory action of TGF- β , progesterone and estrogen on the degradation of cell cycle proteins via the ubiquitin proteasome system (UPS). TGF- β and progesterone block cells in G1 by preventing p27 degradation by the ubiquitin E3 ligase complex, SCF-Cks1/Skp2. This is achieved by increasing the E3-ligase APC-Cdh1, which degrades SCF-Cks1/Skp2. Estrogen increases progression to S phase by degrading p27 via an increase in SCF-Cks1/Skp2. Starting from G1: The phosphatase, Cdc14 removes phosphates from Cdh1 to induce binding to APC. The APC-Cdh1 complex is an E3 ligase that ubiquitinates SCF-Skp2 for proteasomal degradation thereby leaving p27 intact to block cells in G1. Cdk1 phosphorylates Cdh1 causing its degradation by the proteasome. This causes Cdc20 to bind to APC leaving the SCF-Cks1-Skp2 E3 ligase active to degrade p27 for cell cycle progression through S phase. APC bound to Cdc20 ensures progression through G2 to M phase. We show that p27 is an important molecular target for endometrial carcinoma as well as many other human cancers in which p27 is constantly degraded to allow cell proliferation. As general proteasome inhibitors affect degradation of many proteins involved in many physiological and pathological processes, we are exploring specific inhibitors of Skp2 E3 ligase activity to preserve nuclear p27 and regain cell cycle arrest for cancer prevention and therapy.