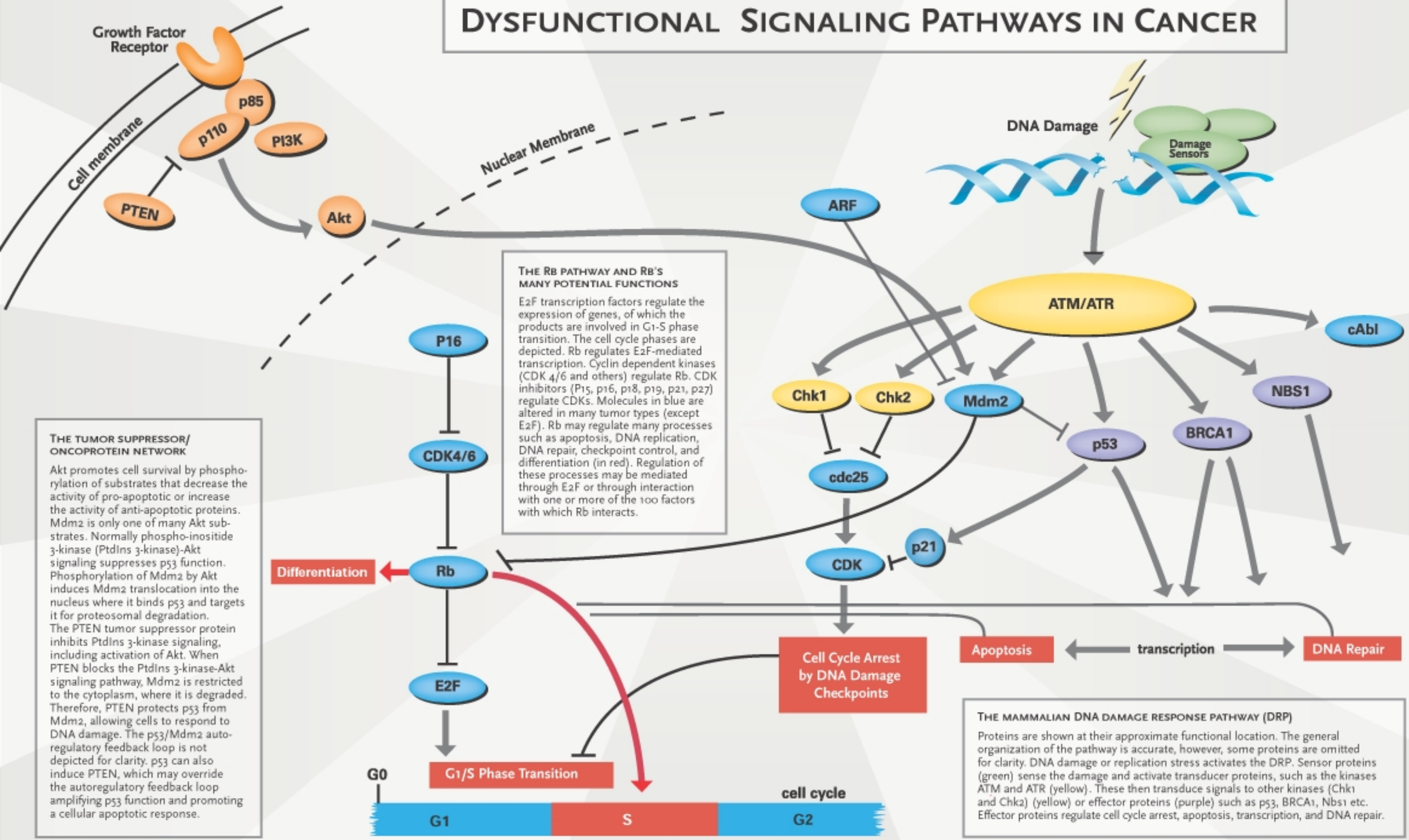
Dysfunctional Signaling Pathways in Cancer



The Rb pathway and Rb's many potential functions

E2F transcription factors regulate the expression of genes, of which the products are involved in G1-S phase transition. The cell cycle phases are depicted. Rb regulates E2F-mediated transcription. Cyclin dependent kinases (CDK 4/6 and others) regulate Rb. CDK inhibitors (P15, p16, p18, p19, p21, p27) regulate CDKs. Molecules in blue are altered in many tumor types (except E2F). Rb may regulate many processes such as apoptosis, DNA replication, DNA repair, checkpoint control, and differentiation (in red). Regulation of these processes may be mediated through E2F or through interaction with one or more of the 100 factors with which Rb interacts.

The tumor suppressor/oncoprotein network

Akt promotes cell survival by phosphorylation of substrates that decrease the activity of pro-apoptotic or increase the activity of anti-apoptotic proteins. Mdm2 is only one of many Akt substrates. Normally phospho-inositide 3-kinase (PtdIns 3-kinase)-Akt signaling suppresses p53 function. Phosphorylation of Mdm2 by Akt induces Mdm2 translocation into the nucleus where it binds p53 and targets it for proteosomal degradation.
The PTEN tumor suppressor protein inhibits PtdIns 3-kinase signaling, including activation of Akt. When PTEN blocks the PtdIns 3-kinase-Akt signaling pathway, Mdm2 is restricted to the cytoplasm, where it is degraded. Therefore, PTEN protects p53 from Mdm2, allowing cells to respond to DNA damage. The p53/Mdm2 autoregulatory feedback loop is not depicted for clarity. p53 can also induce PTEN, which may override the autoregulatory feedback loop amplifying p53 function and promoting a cellular apoptotic response.

The mammalian DNA damage response pathway (DRP)

Proteins are shown at their approximate functional location. The general organization of the pathway is accurate, however, some proteins are omitted for clarity. DNA damage or replication stress activates the DRP. Sensor proteins (green) sense the damage and activate transducer proteins, such as the kinases ATM and ATR (yellow). These then transduce signals to other kinases (Chk1 and Chk2) (yellow) or effector proteins (purple) such as p53, BRCA1, Nbs1 etc. Effector proteins regulate cell cycle arrest, apoptosis, transcription, and DNA repair.