Control and Regulation of the Cell Cycle in Eukaryotic Cells
**MAPK/ERK pathway** Overall, the extracellular *mitogen* binds to the membrane receptor. This allows *Ras* (a GTPase) to swap its GDP for a GTP. It can now activate MAP3K (e.g., Raf), which activates MAP2K, which activates MAPK. MAPK can now activate a transcription factor, such as myc. Receptor-linked *tyrosine kinases* such as the *epidermal growth factor receptor* (EGFR) are activated by extracellular *ligands*. Binding of epidermal growth factor (EGF) to the EGFR activates the tyrosine kinase activity of the cytoplasmic domain of the receptor. The EGFR becomes *phosphorylated* on tyrosine residues. Docking proteins such as *GRB2* contain an *SH2 domain* that binds to the phosphotyrosine residues of the activated receptor. GRB2 binds to the *guanine nucleotide exchange factor* SOS by way of the two SH3 domains of GRB2. When the GRB2-SOS complex docks to phosphorylated EGFR, SOS becomes activated. Activated SOS then promotes the removal of GDP from a member of the *Ras subfamily* (most notably H-Ras or K-Ras). Ras can then bind GTP and become active. Apart from EGFR, other cell surface receptors that can activate this pathway via GRB2 include *Trk A/B, Fibroblast growth factor receptor* (FGFR) and *PDGFR*. 
Mitogen-activated protein kinases (MAPK) are protein kinases that are specific to the amino acids, serine, threonine, and tyrosine. MAPKs belong to the CMGC (CDK/MAPK/GSK3/CLK) kinase group.

MAPKs are involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock and proinflammatory cytokines. They regulate cell functions including proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis.

MAP kinases are found in eukaryotes only.

The closest relatives of MAPKs are the cyclin-dependent kinases (CDKs).
The activation cycle of mammalian Raf protein kinases (simplified overview)

**Relief of autoinhibition**
- In the absence of a cellular stimulus, most Raf molecules are found in the cytoplasm, in a monomeric and "closed" (autoinhibited) state.
- Upon activation, small G-proteins (Ras-GTP) and appropriate ligands are present. Raf will translocate to the membrane, and the internal autoinhibitory interactions will be disrupted, but the kinase is not yet active.

**Dimerization**
- Raf homodimers (partially active) will form homo- or heterodimers (with KSR) with sti bound to the membrane. This will force their activation loops to adopt a partially active conformation via allosteric.

**Transphosphorylation**
- The Raf-Raf (or KSR-Raf) dimers will phosphorylate each other, leading to fully active protein kinases. Other protein kinases such as PAK1 (which is itself activated by GTP-bound Cdc42), can also provide help at this step, with additional phosphorylation events near the N-terminal end of the kinase domain. The phosphorylated activation loops now permanently lock the catalytic site into an active conformation until dephosphorylated.

**MAPK cascade activation**
- MAPK activation (in the cytoplasm) leads to phosphorylation of effector proteins.

**Termination of signaling**
- PP2 dephosphorylates ERK1
- Regulatory phosphatases

**Phosphorylation of effector proteins**
- ERK2 is activated in the cytoplasm
- MAPK activation (in the cytoplasm)

5. Now that Raf is fully active, it can phosphorylate its dedicated substrates, the MKK1 and MKK2 protein kinases. On the other hand, KSR is a rather poor enzyme on MKKs. Once the MKKs are phosphorylated, they become active as well. Freely diffusing in the cytoplasm, the main substrates of MKK1 and MKK2 are ERK1 and ERK2, completing the MAPK cascade.

6. ERK1 and 2 will phosphorylate target substrates of the pathway (including nuclear proteins, such as transcription factors). These are responsible for the cell-cycle promoting effect of Raf pathway.

7. KSR can recruit ERK1 and ERK2 in order to induce a number of inhibitory phosphorylations in the kinase region of Ral and KSR. This feedback will lead to the disruption of the dimers, force dissociation from the membrane and terminate signaling, though several important details are still unknown. In the cytoplasm, phosphatases remove all stimulatory phosphates, leading to inactivation and domain closure.
Mitogen-activated protein kinases are catalytically inactive in their base form. In order to become active, they require (potentially multiple) phosphorylation events in their activation loops. This is conducted by specialized enzymes of the STE protein kinase group.

In the case of classical MAP kinases, the activation loop contains a characteristic TxY (threonine-x-tyrosine) motif (TEY in mammalian ERK1 and ERK2, TDY in ERK5, TPY in JNKs, TGY in p38 kinases) that needs to be phosphorylated on both the threonine and the tyrosine residues in order to lock the kinase domain in a catalytically competent conformation. In vivo and in vitro, phosphorylation of tyrosine precedes phosphorylation of threonine, although phosphorylation of either residue can occur in the absence of the other.

This tandem activation loop phosphorylation (that was proposed to be either distributive or processive, dependent on cellular environment) is performed by members of the Ste7 protein kinase family, also known as MAP2 kinases. MAP2 kinases in turn, are also activated by phosphorylation, by a number of different upstream serine-threonine kinases (MAP3 kinases). Because MAP2 kinases display very little activity on substrates other than their cognate MAPK, classical MAPK pathways form multi-tiered, but relatively linear pathways. These pathways can effectively convey stimuli from the cell membrane (where many MAP3Ks are activated) to the nucleus (where only MAPKs may enter) or to many other subcellular targets.

In comparison to the three-tiered classical MAPK pathways, some atypical MAP kinases appear to have a more ancient, two-tiered system. ERK3 (MAPK6) and ERK4 (MAPK4) were recently shown to be directly phosphorylated and thus activated by PAK kinases (related to other MAP3 kinases).

Inactivation of MAPKs is performed by a number of phosphatases. A very conserved family of dedicated phosphatases is the so-called MAP kinase phosphatases (MKPs), a subgroup of dual-specificity phosphatases (DUSPs). As their name implies, these enzymes are capable of hydrolyzing the phosphate from both phosphotyrosine and the phosphothreonine residues. Since removal of either phosphate groups will greatly reduce MAPK activity, essentially abolishing signaling, some tyrosine phosphatases are also involved in inactivating MAP kinases (e.g. the phosphatases HePTP, STEP and PTPRR in mammals).
MAPKs typically form multi-tiered pathways, receiving input several levels above the actual MAP kinase. In contrast to the relatively simple, phosphorylation-dependent activation mechanism of MAPKs and MAP2Ks, MAP3Ks have stunningly complex regulation. Many of the better-known MAP3Ks, such as c-Raf, MEKK4 or MLK3 require multiple steps for their activation. These are typically allosterically-controlled enzymes, tightly locked into an inactive state by multiple mechanisms. The first step en route to their activation consist of relieving their autoinhibition by a smaller ligand (such as Ras for c-Raf, GADD45 for MEKK4\[8\] or Cdc42 for MLK3\[9\]). This commonly (but not always) happens at the cell membrane, where most of their activators are bound (note that small G-proteins are constitutively membrane-associated due to prenylation). That step is followed by side-to-side homo- and heterodimerisation of their now accessible kinase domains. Recently determined complex structures reveal that the dimers are formed in an orientation that leaves both their substrate-binding regions free. Importantly, this dimerisation event also forces the MAP3 kinase domains to adopt a partially active conformation. Full activity is only achieved once these dimers transphosphorylate each other on their activation loops. The latter step can also be achieved or aided by auxiliary protein kinases (MAP4 kinases, members of the Ste20 family). Once a MAP3 kinase is fully active, it may phosphorylate its substrate MAP2 kinases, which in turn will phosphorylate their MAP kinase substrates.
Activated Ras activates the protein kinase activity of RAF kinase. RAF kinase phosphorylates and activates MEK (MEK1 and MEK2). MEK phosphorylates and activates a mitogen-activated protein kinase (MAPK).

- RAF, and MAPK are both serine/threonine-selective protein kinases. MEK (also known as MAPKK) is a tyrosine/threonine kinase.

In the technical sense, RAF, MEK, and MAPK are all mitogen-activated kinases, as is MNK (see below). MAPK was originally called "extracellular signal-regulated kinases" (ERKs) and "microtubule-associated protein kinase" (MAPK). One of the first proteins known to be phosphorylated by ERK was a microtubule-associated protein (MAP). As discussed below, many additional targets for phosphorylation by MAPK were later found, and the protein was renamed "mitogen-activated protein kinase" (MAPK). The series of kinases from RAF to MEK to MAPK is an example of a protein kinase cascade. Such series of kinases provide opportunities for feedback regulation and signal amplification.

- Three of the many proteins that are phosphorylated by MAPK are shown in the Figure. One effect of MAPK activation is to alter the translation of mRNA to proteins. MAPK phosphorylates 40S ribosomal protein S6 kinase (RSK). This activates RSK, which, in turn, phosphorylates ribosomal protein S6. Mitogen-activated protein kinases that phosphorylate ribosomal protein S6 were the first to be isolated.

- MAPK regulates the activities of several transcription factors. MAPK can phosphorylate C-myc. MAPK phosphorylates and activates MNK, which, in turn, phosphorylates CREB. MAPK also regulates the transcription of the C-Fos gene. By altering the levels and activities of transcription factors, MAPK leads to altered transcription of genes that are important for the cell cycle.
p53 has many mechanisms of anticancer function, and plays a role in apoptosis, genomic stability, and inhibition of angiogenesis. In its anti-cancer role, p53 works through several mechanisms:

- It can activate DNA repair proteins when DNA has sustained damage.
- It can arrest growth by holding the cell cycle at the G1/S regulation point on DNA damage recognition (if it holds the cell here for long enough, the DNA repair proteins will have time to fix the damage and the cell will be allowed to continue the cell cycle).
- It can initiate apoptosis - programmed cell death - if DNA damage proves to be irreparable.
p53 continued

- p53 becomes activated in response to myriad stressors, including but not limited to DNA damage (induced by either UV, IR, or chemical agents such as hydrogen peroxide), oxidative stress, osmotic shock, ribonucleotide depletion, and deregulated oncogene expression. This activation is marked by two major events. First, the half-life of the p53 protein is increased drastically, leading to a quick accumulation of p53 in stressed cells. Second, a conformational change forces p53 to be activated as a transcription regulator in these cells. The critical event leading to the activation of p53 is the phosphorylation of its N-terminal domain. The N-terminal transcriptional activation domain contains a large number of phosphorylation sites and can be considered as the primary target for protein kinases transducing stress signals.

- The protein kinases that are known to target this transcriptional activation domain of p53 can be roughly divided into two groups. A first group of protein kinases belongs to the MAPK family (JNK1-3, ERK1-2, p38 MAPK), which is known to respond to several types of stress, such as membrane damage, oxidative stress, osmotic shock, heat shock, etc. A second group of protein kinases (ATR, ATM, CHK1 and CHK2, DNA-PK, CAK, TP53RK) is implicated in the genome integrity checkpoint, a molecular cascade that detects and responds to several forms of DNA damage caused by genotoxic stress. Oncogenes also stimulate p53 activation, mediated by the protein p14ARF.

- In unstressed cells, p53 levels are kept low through a continuous degradation of p53. A protein called Mdm2 (also called HDM2 in humans), which is itself a product of p53, binds to p53, preventing its action and transports it from the nucleus to the cytosol. Also Mdm2 acts as ubiquitin ligase and covalently attaches ubiquitin to p53 and thus marks p53 for degradation by the proteasome. However, ubiquitylation of p53 is reversible.
• p21 is a potent cdk inhibitor. The p21 (CIP1/WAF1) protein binds to and inhibits the activity of cyclin-CDK2, -CDK1, and –CDK4/6 complexes, and thus functions as a regulator of cell cycle progression at G₁ and S phase. One of the ways it was discovered was as a senescent cell-derived inhibitor.

  The expression of this gene is tightly controlled by the tumor suppressor protein p53, through which this protein mediates the p53-dependent cell cycle G₁ phase arrest in response to a variety of stress stimuli. This was a major discovery in the early 1990s that revealed how cells stop dividing after being exposed to damaging agents such as radiation.

• Studies of human embryonic stem cells (hESCs) commonly report the nonfunctional p53-p21 axis of the G1/S checkpoint pathway, and its relevance for cell cycle regulation and the DNA damage response (DDR). p21 mRNA is clearly present and upregulated after the DDR in hESCs, but p21 protein is not detectable. In this cell type, p53 activates numerous microRNAs (like miR-302a, miR-302b, miR-302c, and miR-302d) that directly inhibit the p21 expression in hESCs.

• p21 can also interact with proliferating cell nuclear antigen (PCNA), a DNA polymerase accessory factor, and plays a regulatory role in S phase DNA replication and DNA damage repair. This protein was reported to be specifically cleaved by CASP3-like caspases, which thus leads to a dramatic activation of CDK2, and may be instrumental in the execution of apoptosis following caspase activation. However p21 may inhibit apoptosis and does not induce cell death on its own.[¹] Two alternatively spliced variants, which encode an identical protein, have been reported.
Schematic representation of cell-cycle regulatory events affected by the MAP-kinase signalling pathway. The Ras-Raf-MEK-MAP-kinase pathway regulates the expression of G1 cyclins and the formation of Cdk±cyclin complexes, the degradation of Cdk-inhibitory molecules, including p27, and the activation of Cdk-activating kinases (CAK; this study), thereby leading to the formation of active cyclin E±Cdk2 complexes which, in turn, promote the re-initiation of DNA synthesis. The nature of additional targets for MAP kinase once Cdk2 is fully active, and prior to the initiation of DNA synthesis, is under current investigation. CycE, cyclin E.
Cyclin-dependent kinases (CDKs) are a family of protein kinases first discovered for their role in regulating the cell cycle. They are also involved in regulating transcription, mRNA processing, and the differentiation of nerve cells. They are present in all known eukaryotes, and their regulatory function in the cell cycle has been evolutionarily conserved. In fact, yeast cells can proliferate normally when their CDK gene has been replaced with the homologous human gene. CDKs are relatively small proteins, with molecular weights ranging from 34 to 40 kDa, and contain little more than the kinase domain. By definition, a CDK binds a regulatory protein called a cyclin. Without cyclin, CDK has little kinase activity; only the cyclin-CDK complex is an active kinase. CDKs phosphorylate their substrates on serines and threonines, so they are serine-threonine kinases. The consensus sequence for the phosphorylation site in the amino acid sequence of a CDK substrate is [S/T*]PX[K/R], where S/T* is the phosphorylated serine or threonine, P is proline, X is any amino acid, K is lysine, and R is arginine.
Cdk1 is a small protein (approximately 34 kilodaltons), and is highly conserved. The human homolog of Cdk1, *CDC2*, shares approximately 63% amino-acid identity with its yeast homolog. Furthermore, human *CDC2* is capable of rescuing fission yeast carrying a *cdc2* mutation. Cdk1 is comprised mostly by the bare protein kinase motif, which other protein kinases share. Cdk1, like other kinases, contains a cleft in which ATP fits. Substrates of Cdk1 bind near the mouth of the cleft, and Cdk1 residues catalyze the covalent bonding of the γ-phosphate to the oxygen of the hydroxyl serine/threonine of the substrate.

In addition to this catalytic core, Cdk1, like other cyclin-dependent kinases, contains a T-loop, which, in the absence of an interacting cyclin, prevents substrate binding to the Cdk1 active site. Cdk1 also contains a PSTAIRE helix, which, upon cyclin binding, moves and rearranges the active site, facilitating Cdk1 kinase activities.

**Cyclin-dependent kinase 1** also known as **CDK1** or **cell division cycle protein 2 homolog** is a highly conserved protein that functions as a serine/threonine kinase, and is a key player in cell cycle regulation. It has been highly studied in the budding yeast *S. cerevisiae*, and the fission yeast *S. pombe*, where it is encoded by genes *cdc28* and *cdc2*, respectively. In humans, Cdk1 is encoded by the *CDC2* gene. With its cyclin partners, Cdk1 forms complexes that phosphorylate a variety of target substrates (over 75 have been identified in budding yeast); phosphorylation of these proteins leads to cell cycle progression.
Cyclin-dependent kinase 2, also known as cell division protein kinase 2, is an enzyme that in humans is encoded by the **CDK2** gene.

- The protein encoded by this gene is a member of the cyclin-dependent kinase family of Ser/Thr protein kinases. This protein kinase is highly similar to the gene products of *S. cerevisiae* cdc28, and *S. pombe* cdc2, also known as Cdk1 in humans. It is a catalytic subunit of the cyclin-dependent kinase complex, whose activity is restricted to the G1-S phase of the cell cycle, and is essential for the G1/S transition. This protein associates with and is regulated by the regulatory subunits of the complex including cyclin E or A. Cyclin E binds G1 phase Cdk2, which is required for the transition from G1 to S phase while binding with Cyclin A is required to progress through the S phase. Its activity is also regulated by phosphorylation. Two alternatively spliced variants and multiple transcription initiation sites of this gene have been reported.

- The role of this protein in G1-S transition has been recently questioned as cells lacking Cdk2 are reported to have no problem during this transition.

- **Inhibitors:** Known CDK inhibitors are p21Cip1 (CDKN1A) and p27Kip1 (CDKN1B).
G1/S-specific cyclin-E1 is a protein that in humans is encoded by the CCNE1 gene.

Like all cyclin family members, cyclin E forms a complex with cyclin-dependent kinase (CDK2). Cyclin E/CDK2 regulates multiple cellular processes by phosphorylating numerous downstream proteins. Cyclin E/CDK2 plays a critical role in the G1 phase and in the G1-S phase transition. Cyclin E/CDK2 phosphorylates retinoblastoma protein (Rb) to promote G1 progression. Hyper-phosphorylated Rb will no longer interact with E2F transcriptional factor, thus release it to promote expression of genes that drive cells to S phase through G1 phase. Cyclin E/CDK2 also phosphorylates p27 and p21 during G1 and S phases, respectively. Smad3, a key mediator of TGF-β pathway which inhibits cell cycle progression, can be phosphorylated by cyclin E/CDK2. The phosphorylation of Smad3 by cyclin E/CDK2 inhibits its transcriptional activity and ultimately facilitates cell cycle progression. CBP/p300 and E2F-5 are also substrates of cyclin E/CDK2. Phosphorylation of these two proteins stimulates the transcriptional events during cell cycle progression. Cyclin E/CDK2 can phosphorylate p220(NPAT) to promote histone gene transcription during cell cycle progression.

Apart from the function in cell cycle progression, cyclin E/CDK2 plays a role in the centrosome cycle. This function is performed by phosphorylating nucleophosmin (NPM). Then NPM is released from binding to an unduplicated centrosome, thereby triggering duplication. CP110 is another cyclin E/CDK2 substrate which involves in centriole duplication and centrosome separation. Cyclin E/CDK2 has also been shown to regulate the apoptotic response to DNA damage via phosphorylation of FOXO1.
Cell division protein kinase 6 (CDK6) is an enzyme encoded by the CDK6 gene. It is regulated by cyclins, more specifically by Cyclin D proteins and Cyclin-dependent kinase inhibitor proteins. The protein encoded by this gene is a member of the cyclin-dependent kinase, (CDK) family, which includes CDK4. CDK family members are highly similar to the gene products of Saccharomyces cerevisiae cdc28, and Schizosaccharomyces pombe cdc2, and are known to be important regulators of cell cycle progression in the point of regulation named R or restriction point. This kinase is a catalytic subunit of the protein kinase complex, important for the G1 phase progression and G1/S transition of the cell cycle and the complex is composed also by an activating sub-unit; the cyclin D. The activity of this kinase first appears in mid-G1 phase, which is controlled by the regulatory subunits including D-type cyclins and members of INK4 family of CDK inhibitors. This kinase, as well as CDK4, has been shown to phosphorylate, and thus regulate the activity of, tumor suppressor Retinoblastoma protein making CDK6 an important protein in cancer development.
The protein encoded by this gene is a member of the cyclin-dependent kinase (CDK) family. CDK family members are highly similar to the gene products of S. cerevisiae cdc28, and S. pombe cdc2, and known as important cell cycle regulators. This kinase was found to be a component of the multiprotein complex TAK/P-TEFb, which is an elongation factor for RNA polymerase II-directed transcription and functions by phosphorylating the C-terminal domain of the largest subunit of RNA polymerase II. This protein forms a complex with and is regulated by its regulatory subunit cyclin T or cyclin K. HIV-1 Tat protein was found to interact with this protein and cyclin T, which suggested a possible involvement of this protein in AIDS. CDK9 is also known to associate with other proteins such as TRAF2, and be involved in differentiation of skeletal muscle.
The diagram shows the role of Cdk1 in progression through the *S. cerevisiae* cell cycle. Cln3-Cdk1 leads to Cln1,2-Cdk1 activity, eventually resulting in Clb5,6-Cdk1 activity and then Clb1-4-Cdk1 activity.
Regulation of the G₁/S transition. Mitogenic signals promote the assembly of active cyclin D-dependent kinases containing either CDK4 (or CDK6; not shown) and a Cip or Kip protein. Sequestration of Cip/Kip proteins lowers the inhibitory threshold and facilitates activation of the cyclin E–CDK2 complex. The cyclin D- and E-dependent kinases contribute sequentially to Rb phosphorylation, canceling its ability to repress E2F family members and activating genes required for entry into S phase. The latter include cyclins E and A, as well as a bank of gene products that regulate nucleotide metabolism and DNA synthesis per se. Cyclin E–CDK2 antagonizes p27 by phosphorylating it and triggering its proteolysis. The degradation of Cip/Kip proteins and the induction of cyclins by E2F (highlighted by background shading) contribute to mitogen independence and to the irreversibility of the transition.
p16 (also known as cyclin-dependent kinase inhibitor 2A, multiple tumor suppressor 1 and as several other synonyms), is a tumor suppressor protein, that in humans is encoded by the CDKN2A gene. p16 plays an important role in cell cycle regulation by decelerating cells progression from G1 phase to S phase, and therefore acts as a tumor suppressor that is implicated in the prevention of cancers, notably melanoma, oropharyngeal squamous cell carcinoma, and esophageal cancer. The CDKN2A gene is frequently mutated or deleted in a wide variety of tumors.

p16 is an inhibitor of cyclin dependent kinases such as CDK4 and CDK6. These latter kinases phosphorylate retinoblastoma protein (pRB) which eventually results in progression from G1 phase to S phase.
• The \( p27^{\text{Kip1}} \) gene has a DNA sequence similar to other members of the "Cip/Kip" family which include the \( p21^{\text{Cip1/Waf1}} \) and \( p57^{\text{Kip2}} \) genes. In addition to this structural similarity the "Cip/Kip" proteins share the functional characteristic of being able to bind several different classes of Cyclin and Cdk molecules. For example, \( p27^{\text{Kip1}} \) binds to cyclin D either alone, or when complexed to its catalytic subunit CDK4. In doing so \( p27^{\text{Kip1}} \) inhibits the catalytic activity of Cdk4, which means that it prevents Cdk4 from adding phosphate residues to its principal substrate, the retinoblastoma (pRb) protein. Increased levels of the \( p27^{\text{Kip1}} \) protein typically cause cells to arrest in the G1 phase of the cell cycle. Likewise, \( p27^{\text{Kip1}} \) is able to bind other Cdk proteins when complexed to cyclin subunits such as Cyclin E/Cdk2 and Cyclin A/Cdk2.

• In general, extracellular growth factors which promote cell division reduce transcription and translation of \( p27^{\text{Kip1}} \). Also, increased synthesis of CDK4,6/cyclin D causes binding of \( p27 \) to this complex, sequestering it from binding to the CDk2/cyclin E complex. Furthermore, an active CDK2/cyclin E complex will phosphorylate \( p27 \) and tag \( p27 \) for ubiquitination, A mutation of this gene may lead to loss of control over the cell cycle leading to uncontrolled cellular proliferation. Loss of \( p27 \) expression has been observed in metastatic canine mammary carcinomas. Decreased TGF-beta signalling has been suggested to cause loss of \( p27 \) expression in this tumor type.

• A structured cis-regulatory element has been found in the 5' UTR of the P27 mRNA where it is thought to regulate translation relative to cell cycle progression.

• P27 regulation is accomplished by two different mechanisms. In the first its concentration is changed by the individual rates of transcription, translation, and proteolysis. P27 can also be regulated by changing its subcellular location. Both mechanisms act to reduce levels of p27, allowing for the activation of Cdk1 and Cdk2, and for the cell to begin progressing through the cell cycle.
Apoptosis; programmed cell death

Apoptosis signaling pathways mediated by TNFR, Fas, or mitochondria. Death receptor–mediated and mitochondrial-mediated pathways are two principal signaling pathways of apoptosis. Activation of death receptors resulted in the recruitment of adaptor proteins through interaction of death domain (DD). Recruitment of FADD to Fas or to TNFR through TRADD activates initiator caspase-8. Stimuli other than death receptor activation, such as anticancer drugs, radiation, and reactive oxygen radicals, etc., triggering apoptotic pathways initiate at mitochondria. Cytochrome c is released into the cytosol from mitochondria and binds to Apaf1 with adenosine triphosphate (ATP), resulting in the activation of caspase-9. The activation of caspase-8 or caspase-9 leads to the activation of the caspase cascade. The NF-κB signal transduction pathway was also initiated through the interaction of TRADD and TRAFs. The activated NF-κB promotes the transcription of IAPs, as well as proinflammatory cytokines. IAPs block caspase-3, caspase-7, and caspase-9 directly, also inhibiting caspase-8 along with TRAFs. The precise functions of IAPs remain to be addressed in the future.
Bcl-2 (B-cell lymphoma 2), encoded in humans by the BCL2 gene, is the founding member of the Bcl-2 family of regulator proteins that regulate cell death (apoptosis), by either inducing (pro-apoptotic) it or inhibiting it (anti-apoptotic). Bcl-2 is specifically considered as an important anti-apoptotic protein and is thus classified as an oncogene. Bcl-2 derives its name from B-cell lymphoma 2, as it is the second member of a range of proteins initially described in chromosomal translocations involving chromosomes 14 and 18 in follicular lymphomas. Orthologs (such as Bcl2 in mice) have been identified in numerous mammals for which complete genome data are available. The two isoforms of Bcl-2, Isoform 1, also known as 1G5M, and Isoform 2, also known as 1G5O/1GJH, exhibit similar fold. However, results in the ability of these isoforms to bind to the BAD and BAK proteins, as well as in the structural topology and electrostatic potential of the binding groove, suggest differences in antiapoptotic activity for the two isoforms. Like BCL3, BCL5, BCL6, BCL7A, BCL9, and BCL10, it has clinical significance in lymphoma.