Tumor protein p53

Tumor protein p53 is a tumor suppressor that prevents cells from dividing and signals them to undergo apoptosis if they sustain irreparable DNA damage.

Protein: p53 (approximately 53 kDa)

Location

Chromosome 17p13.1

Often called the “guardian of the genome” due to its critical role in maintaining genomic stability.

⚙ Key Functions

DNA Damage Response

p53 is activated when DNA is damaged, helping to prevent the propagation of mutations.

Cell Cycle Arrest

Stops the cell cycle (especially at the G1/S checkpoint) to allow time for DNA repair.

Apoptosis (Programmed Cell Death)

If the DNA damage is too severe, p53 initiates apoptosis to eliminate the damaged cell.

Senescence

Induces a permanent state of growth arrest in aging or stressed cells.

DNA Repair

Stimulates the expression of genes involved in repair mechanisms.

Regulation

Normally kept in check by MDM2, a protein that promotes p53 degradation.

Stabilized and activated in response to stress, allowing it to accumulate in the nucleus and act as a transcription factor.

Clinical Significance

TP53 gene mutation is among the most common mutations in human cancers.

Mutant p53 often loses its tumor-suppressive functions and can even gain oncogenic properties.

Immunohistochemistry (IHC) for p53 is often used in pathology to infer TP53 mutation status.

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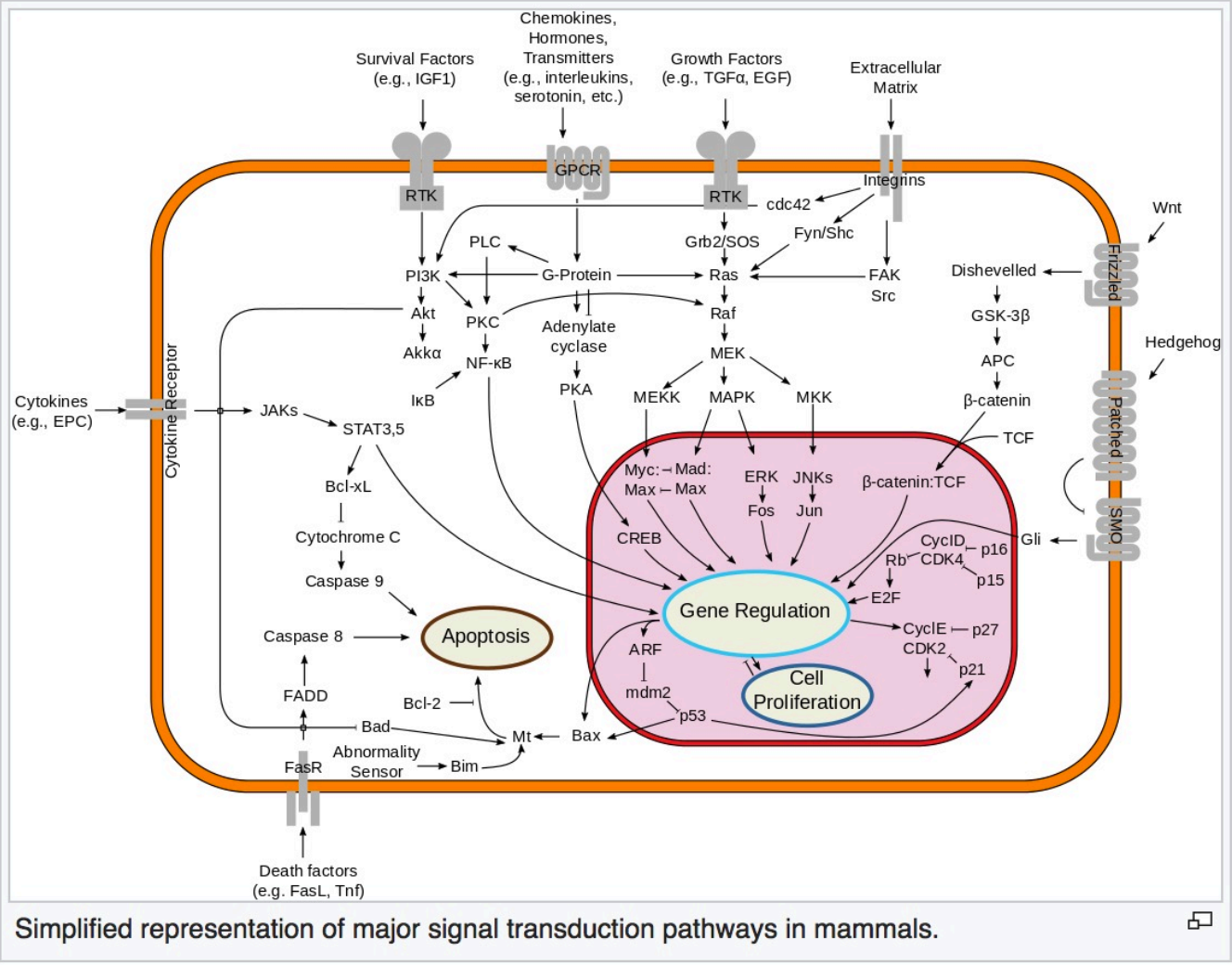
p53, cellular tumor antigen p53, phosphoprotein p53, or tumor suppressor p53, is a protein that in humans is encoded by the TP53 gene.

The p53 protein is crucial in multicellular organisms, where it regulates the cell cycle and, thus, functions as a tumor suppressor, preventing cancer. As such, p53 has been described as “the guardian of the genome” because of its role in conserving stability by preventing genome mutation.

The expression of BAX is upregulated by the tumor suppressor protein p53, and BAX has been shown to be involved in p53-mediated apoptosis



Simplified representation of major signal transduction pathways in mammals.

Hence TP53 is classified as a tumor suppressor gene.

Mutation of p53 is an atypical genetic change that occurs during tumorigenesis. Thus, a potential

correlation may exist between tumor location and p53 status.

Statistical analysis demonstrated that the left medial temporal lobe and right anterior temporal lobe were specifically associated with high expression of mutant p53. Kaplan-Meier curves showed that tumors located in these regions were associated with significantly worse progression-free survival compared with tumors occurring elsewhere, providing new evidence that genetic changes during cancer may have anatomic specificity. Additionally, suggests that tumor location identified on structural MR images could potentially be used for customized presurgical outcome prediction [1].

p53 causes tumor regression by suppressing tumor proliferation and indirectly induces involution of tumor vessels by fostering unopposed activity of Angiopoietin 2 in an environment of diminishing VEGF [2].

Alterations of the TP53 tumor suppressor gene occur in ~30% of primary glioblastoma (Glioblastoma) with a high frequency of missense mutations associated with the acquisition of oncogenic “gain-of-function” (GOF) mutant (mut)p53 activities. PRIMA-1MET/APR-246, emerged as a promising compound to rescue wild-type (wt)p53 function in different cancer types. Previous studies suggested the role of wtp53 in the negative regulation of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT), a major determinant in resistance to therapy in Glioblastoma treatment. The potential role of MGMT in expression of p53 and the efficacy of PRIMA-1MET with respect to TP53 status and expression of MGMT in Glioblastoma remain unknown. We investigated response to PRIMA-1MET of wtp53/MGMT-negative (U87MG, A172), mutp53/MGMT-positive U138, LN-18, T98/Empty vector (T98/EV) and its isogenic MGMT/shRNA gene knockdown counterpart (T98/shRNA). We show that MGMT silencing decreased expression of mutp53/GOF in T98/shRNA. PRIMA-1MET further cleared T98/shRNA cells of mutp53, decreased proliferation and clonogenic potential, abrogated the G2 checkpoint control, increased susceptibility to apoptotic cell death, expression of GADD45A and sustained expression of phosphorylated Erk1/2. PRIMA-1MET increased expression of p21 protein in U87MG and A172 and promoted senescence in U87MG cell line. Importantly, PRIMA-1MET decreased relative cell numbers, disrupted the structure of neurospheres of patient-derived Glioblastoma stem cells (GSCs) and enabled activation of wtp53 with decreased expression of MGMT in MGMT-positive GSCs or decreased expression of mutp53. Our findings highlight the cell-context dependent effects of PRIMA-1MET irrespective of p53 status and suggest the role of MGMT as a potential molecular target of PRIMA-1MET in MGMT-positive GSCs [3].

The giant cell glioblastoma is a histological variant of glioblastoma, presenting a prevalence of bizarre, multinucleated (more than 20 nuclei) giant (up to 400 µm diameter) cells.

It occasionally shows an abundant stromal reticulin network and presents a high frequency of TP53 gene mutations.

p53 Inhibition

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1)
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2)
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