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https://www.100test.com/kao_ti2020/462/2021_2022__E9_98_85_E8_AF_BB_E8_BE_85_E5_c81_462953.htm What is p53 ? After the identification of the p53 protein and the subsequent cloning of p53 genes from several species, early observations suggested that p53 may function as an oncogene, because overexpression of p53 appeared to cause oncogenic transformation of cells. In the late 1980s, however, several critical discoveries defined the normal function of p53 to be anti-oncogenic. Wild-type p53 genes, when introduced into cells, were found to be growth suppressive. The screening of DNA from colon cancer patients revealed that p53 mutations occur with unusually high frequency in tumor tissue, an observation that was extended to most of the other major forms of human cancer. Indeed, members of Li-Fraumeni cancer-prone families were shown to carry germ-line p53 mutations. The importance of these observations was underscored by the finding that mice that are homozygous null for p53, although developmentally competent, are highly predisposed to tumors. The functional character of the p53 protein was determined by experiments showing that p53 contains a strong transcriptional activation domain within its amino terminus and that it is a tetrameric, sequence-specific DNA-biding protein with a defined cognate binding site containing two copies of the 10-mer (5-RRRCA/TT/AGYYY-3). Although the p53 protein acts as a transcriptional activator of genes containing p53-binding sites, it is also capable of strongly inhibiting transcription from many genes

lacking p53-binding sites. Several oncogenic DNA viruses express viral gene products that associate with and inhibit the trans-activation function of p53, notably SV40 large T antigen, the adenovirus E1B 55-kD protein, and the E6 protein of oncogenic forms of human papillomavirus (HPV E6). In cells, p53 can associate with a 90-kD protein, identified as the product of the mdm-2 oncogene, which is amplified in some types of tumors. When bound to mdm-2, p53 can no longer function as an activator of transcription. p53 plays multiple roles in cells. Expression of high levels of wild-type (but not mutant) p53 has two outcomes: cell cycle arrest or apoptosis. The observation that DNA-damaging agents induce levels of p53 in cells led to the definition of p53 as a checkpoint factor, akin, perhaps, to the product of the fad9 gene in yeast. While dispensable for viability, in response to genotoxic stress, p53 acts as an "emergency brake" inducing either arrest or apoptosis, protecting the genome from accumulating excess mutations. Consistent with this notion, cells lacking p53 were shown to be genetically unstable and thus more prone to tumors. (中文版)p53是存在人胞的一抗癌白，它有抑制胞生及持物完整性的功能。事上，半以上的癌症胞都有p53的突，可其在胞生控制上扮演了重要的角色。在正常下，p53的半衰期只有30分，相不定；然而胞紫外，子化射(如X光，伽照射)，或胞缺氧、缺，p53被活化，同它的定性提高，造成胞的p53大量增加，除了上述刺激外，化治上常用的物也有同效。p53的活化增加常致可能的果：一是胞停止在G1或G2期；另一是胞自行（apoptosis)而死亡。胞由此得以修(前者)，或度受的胞得以人除去(後者)。

依p53的"自措施"在一些胞中常因p53的突而失去功能，使得些有"缺陷"的胞能不受控制的生分裂，致突的累和癌症的生。然境因子影p53活性及定性的事已知已久，其的分子仍不清楚。蛋白的磷酸化(phosphorylation)一向被在息上扮演重要的角色。事上，由我及其他室的研究，p53在紫外，伽射照射後，其N端的胺基酸(第15，20，33，37)有磷酸化的象。磷酸化生快速，乎是在照射後分即已生，而持多久胺基酸位置、刺激型，及胞而。至於些磷酸化p53的反之性仍有待明。最近我有在胞分裂(Cell cycle)的查(checkpoint)上扮演著重要控功能的磷酸化酵素(kinase) hCHK1，CHK2可以有效的磷酸化p53。有趣的是，磷酸化的胺基酸中包括了那些可以被紫外、伽引起的位置，即第15，20及37胺基酸。我正著手研究可能的CHKs的上游分子及p53在CHKs磷酸化後功能之化。此外， 不同的境因子p53的方式可能各，有些可能透磷酸化以外的方式行。我希望能先定出p53序列中境因子互有的域(domain)，再由此找出p53定性有的制及分子。 