The structure of protein p53 biology essay

Protein p53, encoded by gene Tp53, is known as a tumor suppressor. Discovered in 1979 as a transformation-related protein (DeLeo et al., 1979) and protein which accumulates in the tumor cells binding with simian virus 40 (SV40) large T antigens (Lane et al., 1979), p53 was regarded as an important protein in the regulation of an apoptosis and cancerization. During the last 30 years, a large amount of studies was taken in p53 and its related mechanisms in cellular process. In 1980s, researchers cloned the Tp53 gene and determined the role of p53 as a tumor suppressor. However, the structure of p53 protein was uncertain until 2006, in which William and his colleagues determined the DNA binding core domain of protein p53 (William. C. Ho. et al., 2006). Plenty of researches focus on the regulatory mechanism of p53 and hundreds types of targets and regulators of p53 were found, e. g. MDM2, Cyclin H, ATR, ATM, etc. These molecules can interact with p53 and regulate the life process collectively.

P53 plays a very crucial role in cell cycle regulation and apoptosis induction, the mutation of p53 would lead to the cancerization in cells and induce cancer. Bai and Zhu (2006) reported that the mutation or loss of p53 gene and protein can be found in over 50% of tumor cells in human all around the world. For these reasons, the application of cancer therapy through protein p53 and Tp53 gene is a very potential aspect in cancer treatment. This review will describe the structure and function of p53 protein, examine its role in natural and tumor cells and focus on the cancer therapy application through p53.

The Structure of P53

Human protein p53 is a 53KDa phosphoprotein encoded by a 20Kb-gene; it has an intricate structure which is closely related to its function. Wild-type P53 protein contains five major domains. The N-terminus of p53 is a transcription-activation domain (TAD), with a major one at residues 1-42 and a minor one at residues 55-75 (Venot et al., 1998). The basic function of this domain is involvement in the regulation of the pro-apoptotic transcription. Following the TAD is a proline-rich region which plays an important role in apoptotic activities. The central core of p53 protein is a DNA binding domain which can bind and interact with special DNA sequence that contain 2 copies of 10bp motif 5′-PuPuPuC(A/T)-(T/A)GPyPyPy-3′ (Kern et al., 1991). This region is also responsible for binding with LMO3, which is an essential co-repressor of p53 (Larsen et al., 2010). A nuclear localization signaling domain (NLS) is located beside the C-terminus of central core. The C-terminus domain of p53 protein, called negative regulatory domain is involved in the down regulation of DNA binding in central core (Chen, et al., 2005), and is also an essential part for the induction of cell death. A homo-oligomerisation domain (OD) located between the negative regulatory domain and NLS. This part is involved in tetramerization, which is a main activity for p53 in vivo. The different domains of p53 protein have their functions respectively, nevertheless, they constitute an inseparable entirety to play the role as a tumor suppressor.

The function of p53

As a cancer suppressor, the main function of p53 is the anticancer function. P53 plays a vital role in apoptosis, gene stability and DNA damage through a

series of complex mechanisms. First, p53 can respond to DNA damage through activating the DNA repair protein. For example, upon DNA damage, p53 gets activated and initiates the transcription of repair protein XPC and DDB2. The complex of p53-XPC-DDB2 can repair the DNA damaged by UV (Adimoolam and Ford, 2003). In addition, p53 can arrest the cell cycle at S, G1, and G2 phase (Agarwal et al., 1995), which can provide sufficient time for proteins repair to fix the damaged DNA.

Induction of apoptosis, the programmed cell death, is also the essential and most important anti-cancer function of p53. If DNA damage is irreparable, p53 can activate the expression of pro-apoptosis genes like p21, Gadd45 (growth arrest and DNA-damageinducible protein 45), Bcl-2 family, etc. Moreover, p53 can bind and interact with hundreds of protein to regulate the cellular process and apoptosis. P53 can also restrain the cell cycle by repressing the expression of genes include bcl-2, bcl-X, cyclin B1, MAP4 and survivin (Bai and Zhu, 2006). The physiological functions of p53 are to maintain the genetic stability and regulate the normal cell cycle through a complex regulatory network. The mutation of Tp53 gene would lead to the loss of function of p53 protein, resulting in a cellular canceration. Consequently, the essential function of p53 is preventing the cancerization of cells by repairing genes or inducing apoptosis, in order to achieve these function, p53 can interact with a number of downstream targets.

The Regulation in P53 Level

A large amount of cellular response and process is induced by p53 through a series of complex biochemical mechanisms. P53 achieves its function through activating, binding, interacting with myriad kinds of downstream

target molecules including kinase, enzymes, etc. Generally, p53 interacts with its target by phosphorylation of transcription-activation domain in N-terminus.

The most well-known target of p53 is a cyclin-dependent kinase (CDK) p21. P53 would initiate the transcription and transduction of p21 in response to cellular stress, p21 is necessary in G1 control, the increase of p21 arrest the cell growth and induce cell death (Yin, et al., 1999). P53 and p21 contribute to a cell-cycle check point in G1 phase. The damaged genes would not be allowed to express until they are repair. If most damaged genes cannot be repaired, the accumulation of p21 regulated by p53 would induce apoptosis.

Another important target of p53 is MDM2 (also called HDM2 in human body). MDM2 is a p53 inducible gene and its product can bind and interact with p53. The product of MDM2 gene, called p90 or p95, can bind with p53 and combine with ubiquitinate which can induce the degradation of p53 (Buschmann, et al., 2000). MDM2 is the killer of p53 which can keep the amount of p53 proteins into an appropriate level. However, a series of cellular stress would cause the overexpress of MDM2 and result in the over degradation of p53, the cell would lose ground and transform to tumor cell.

P53 has plenty of other regulation pathways that cannot be listed in detail. The hundreds of pathways regulated by p53 have two mutual purposes: repair genes and induction of apoptosis. Therefore, the core of the p53 regulation levels is to maintain the stability of genes and accelerate the death of damaged or diseased cells.

The Role of p53 in Normal and Tumor cells

In natural human cells, the wt-p53 protein can be regarded as a guardian of the cell and genome. It can monitor the vital process, repair the gene indirectly through interaction with repair protein and induce apoptosis when necessary (Hofseth, et al., 2004). P53 plays a crucial role in numerous cellular processes which are related to cell cycle and cell death. If Tp53 gene mutated, the tumor suppression function in the cell would partly reduce. As a result, people whose Tp53 gene was mutated are more susceptible to suffer from cancer.

Tp53 gene is mutated in over half of tumor cells; the mutation would alter the structure of p53 protein, thus p53 would lose its function partly or completely. The p53-mutated cells can not die programmatically, and become tumor cells. The mutated p53 protein tends to accumulate in tumor cells because the mutated p53 lose its function to induce the express of MDM2, which can degrade p53 proteins in the cell. The accumulation of p53 protein is a significant feature for the tumor cells. In cancer treatments, tumor cells can be detected through the accumulation of p53. However, mutated p53 can also be an obstacle of the therapy because mutant p53 can inhibit the function of wide-type p53 (Blagosklonny, M. V., 2002). If the treatment strategy is transferring the wide-type p53 into tumor cells, how to eliminate the effect of mutant p53 is the problem which has to be solved first. Consequently, p53 plays crucial roles both in normal cells and tumor cells; it is a gatekeeper in normal cells and a marker for tumor cells; it is an effective target for cancer treatments, nevertheless it can also become a barrier in cancer therapy.

Conclusion

P53 is the best-known transcription factor and cancer suppressor plays multiple roles in the cell. In healthy cells and, it is a gatekeeper to monitor the cell cycle and prevent the mutation of gene. If some mutations happen in the genome, p53 serve as a “ doctor” to activate the repair process of damaged genes. When cells suffer from an irreversible damage or oncogenic stress, p53 can become a killer of cancerous cells. P53 participates in a number of biochemical pathways which can respond to the stress, arrest cell-cycle, repair gene and induce apoptosis. In the 30 years after the discovery of p53, plenty investigation was devoted into this essential protein and received a number of great achievements. A large amount of downstream targets has been identified and the regulatory network of p53 levels became clearer. Although plenty of details about p53, such as the relationship between each pathway, are still unknown. There is still a potential application through p53 in cancer treatments.