

p53: Hero or Villain

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The tumor suppressing protein, p53, is a widely studied subject of which loads of knowledge has been gained but overall it is still a mystery. The p53 protein has many roles in the cell, some of which are activation of cell cycle arrest, senescence, and differentiation. The interesting information about p53 that really brings this particular protein to the attention of many people however is its ability to selectively destroy stressed, abnormal, or damaged cells. These techniques possessed by the protein thereby help the system to prevent cancer development. p53 can also lead to severe cell degradation if it is not closely regulated. Many instances can lead to these occurrences, even events where p53 brings it on itself. Here we will look into what stimulates the actions of the p53 and reasons behind why it works the way it does.

Introduction

Regulation of p53

Because p53 works so well at inhibiting abnormal growth, it is also necessary to ask the question, “Does this protein inhibit only cancerous cells or can it also inhibit perfectly healthy cells?” Regulation of the p53 protein is essential during maturation and the growth periods of all cells. A key component in the regulation of p53 is another protein called MDM2. MDM2 is an ubiquitin ligase, also known as a regulator, which recognizes the N-terminal trans-activation domain (TAD) of the p53 tumor suppressor and acts as an inhibitor of p53 transcriptional activator. This interaction keeps the p53 levels low while maturation and growth periods of the cell are taking place. Interestingly enough, MDM2 is a transcriptional target of p53 so in turn p53 actually regulates itself (Sherr & Webber, 2000).

Another interesting discovery consistent with regulation of p53 is the presence of the ARF protein. ARF is another tumor suppressing protein found within the nucleus that actually builds up and forms stable complexes with MDM2. This allows the p53 to build up in the nucleus, which comes as a result of ARF and MDM2 inhibiting the ubiquitination of p53, usually occurring after growth and maturation of the cell takes place (Vousden, 2000)

Not only is p53 regulated by other proteins, but it is also regulated by means of where it is located within the cell. Because p53 works as a transcription factor, its

location in perspective to the nucleus puts limits on what it can and cannot do. There are many mechanisms that regulate the entrance and exit of p53 to and from the nucleus. For it to be transported into the nucleus, there are two possible ways. The first way p53 can be transported into the nucleus is by dynein, which is a motor protein that can transport cellular cargo, and the microtubule network which requires the N-terminus of p53. The second way that p53 can be transported into the nucleus is if the amino-acids at the end of the chain, also known as C-terminus, let off the signals that contain which alert the nuclear import factors. In turn the N-terminal nuclear export signal is regulated by phosphorylation, which can turn protein enzymes on and off thereby altering their function and or activity.

Phosphorylation inhibits the nuclear export sequence which causes the N-terminal p53 phosphorylation to retain p53 in the nucleus. When this happens it's like the two acts against each other firstly by inhibiting the N-terminal export signal, and secondly by inhibiting the binding of MDM2 and ultimately reducing the ubiquitination and activation of the C-terminal export signal. With these things happening along with the regulatory mechanisms mentioned earlier, a cell is able to regulate p53 at a healthy level (Sutcliffe & Brehm, 2004). The methods of phosphorylation and dephosphorylation are described in Figure 1.

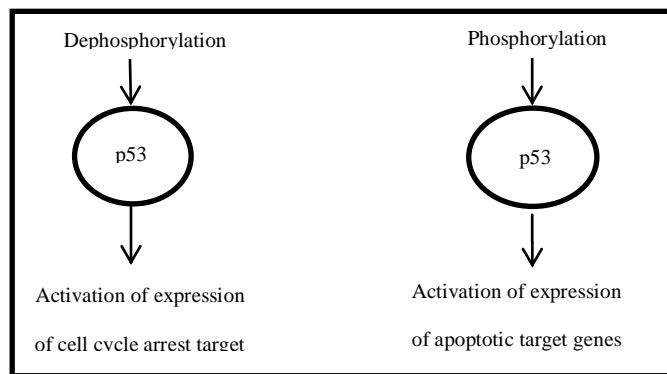


Figure 1.

p53 and Apoptosis

When p53 is activated we then need to understand how it functions and particularly what pathways it takes to complete apoptosis. p53's ability to repress transcription is one of its most significant ways that it can induce apoptosis but exactly how the protein goes about doing this is still unknown. p53 has the ability to engage all of the apoptotic pathways in a cell. It can stimulate both the death receptor signals as well as turn on the mitochondrial perturbations, known as disturbers, which include the release of cytochrome c.

In the recent past there have been many p53 transcriptional targets encode proteins which localize to the mitochondria and in turn affect the mitochondrial membrane potential, a process that sends a strong apoptotic signal through this pathway. These proteins include Noxa, a protein that contains a BH3 domain which can interact with the antiapoptotic Bcl2 protein, and p53AIP1, which is a novel protein with no known homologs.

Recently, a new death receptor protein has been added which is named PIDD, which is a death domain that contains large amounts of protein, which has the possibilities to bind with the complexes that stimulate the death receptor proteins. It is very important to understand that these are not the only apoptotic genes that can be targeted by p53. These new members of the p53-inducible club have passed the acid test to be considered true mediators of p53 apoptosis. This means that each of the genes has been shown to be required for the full apoptotic response to take place, under most conditions at the least. Most of this evidence has been gained from antisense experiments, which are often complicated by the lack of reliable methods for selecting effective antisense sequences leading to unknowns, in tissue culture cells.

Recent Progress

While the p53 protein is essential to a healthy lifestyle, it also has its negatives. If the protein is in short supply then the possibilities of cancerous tumors coming about is

greatly increased. If the supply of p53 is higher than what it should be then it can lead to degradation of perfectly healthy cells. Also, if the supply of the p53 protein is in excess during the growth and maturation of cells, then growth can be stunted and the procedure will not go as it should. Increasing the amount of p53, which may initially seem a good way to treat tumors or prevent them from spreading, is in actuality not a usable method of treatment, since it can cause premature aging. However, restoring endogenous p53 function holds a lot of promise. Loss of p53 creates genomic instability that most often results in the aneuploidy phenotype, which is an abnormal number of chromosomes, and is a type of chromosome abnormality.

Discussion

Very commonly, cancer is associated with a loss of function of the p53 protein. The tumor suppressor p53 is mutated in more than 50% of human cancers and studies go on to show that if we can one day understand and be able to regulate this protein, then the possibilities of humans dying from cancer will greatly go down if not cease to exist.

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