Microreviews in Cell and Molecular Biology 2012

Relationship of DNA Regulation Processes in Different Repair Mechanisms

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Key Words:
DNA replication, DNA damage, p53 protein, repair mechanism, growth serum, growth stimulation

During the process of DNA replication, vulnerability to DNA damage increases. This creates a problem that our bodies complex physiological process can offer a solution to. Recent studies have uncovered five major DNA repair mechanisms that are regulated by specific gene expression: the nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), homologous recombination repair (HRR) and nonhomologous end joining (NHEJ). The articles I have chosen to review show relationships between the specific DNA repair genes and also how they relate to entire repair mechanisms. The importance of uncovering how complex the homeostatic regulation of DNA repair is could lead us to uncover specific genes or other regulatory malfunctions that promote tumorgenisis, and thus provide more insight to prevent the spread of cancer. Recent progress has been made in uncovering a specific protein, p53, which has a pivotal role in the cellular stress response. P53 acts as a promoter for cellular stress responses such as BER and NER. Once it has been activated, however, there are also processes that it undergoes that must deactivate the protein in order for the cell to continue the growth process. Also, in recent reseach, the relationship between growth stimulation and DNA repair genes was observed. Repair genes that couple with MMR and HRR were tested to observe the effect of growth stimulation on their expression. Alongside this research, another article discusses the wild type p53-induced phosphotase acts as a critical homeostatic regulator of the DNA damage response (DDR). The current status of knowledge in this area is limited due to the complexity of feedback processes that occur during all the stages of DNA repair. Thereby opening up opportunities for future research in this area of cell biology.

Introduction

The collective processes of DNA repair aim to identify and fix damage that has occurred to DNA molecules. Factors that can cause DNA damage include UV light, radiation, as well as malfunctions in normal metabolic processes. These factors result in lesions that can alter the cells ability to correctly transcribe the genome. Mutations also occur that prevent efficient cellular function, thereby affecting the further proliferation of daughter cells. The many avenues that DNA damage can take are why the DNA process is complex and continuously ongoing. The fascinating thing about the DNA repair processes is its use of different mechanisms to repair itself specifically according to the type of damage. Each specific repair mechanism is regulated as well as turned on and off by proteins, specific enzymes, as well as genes that encode specifically during different types of repair. These DNA repair regulators have also been topics of research that identify a number of different functions specific to the regulator. These research topics also serve to identify its presence in multiple repair mechanisms. DNA processes have the ability to fail, which can cause unfixable damage such as DNA cross linkages and double strand breaks. Our bodies mechanisms in which it repairs, therefore, are

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crucial to understand because of the potential to identify exactly how permanent DNA damage can be avoided.

Recent Progress

In "Homeostatic Regulation of Base Excision Repair by a p53-induced phosphotase", the p53 protein is specifically observed and tested to uncover how it is activated and deactivated, and what the specific effector molecules are. P53 was shown to actively promote NER by activation of NER genes such as *Gadd45, DDB2* and *XPC*. Also, p53 increases DNA cleavage molecule efficiency by binding during BER. This displays how a single protein can be used for multiple DNA processes in the body. The protein, p53, however, must be negatively regulated in order for the cell to stop the repair process, restart the cell growth cycle, and restore homeostasis. A major key component of this feedback loop, ligase MDM2-p53, serves to help facilitate p53 in proteolytic degradation by binding to the protein. The continual binding also causes the half-life of the p53 protein to decrease, which presents a problem when DNA damage needs quick repair. A solution provided by our bodies complex repair system is presented by phosphorylation of both MDM2 (murine double minute oncogene) and p53 by the ATM (ataxia telangiectasia mutated) kinase. This phosphorylation inhibits the binding of MDM2 to p53 and allows it to continue the process of cellular repair. The discussion of two of my articles fell upon a specific component of this cellular repair feedback loop. The target gene PPM1D, also known as *Wip1* (wild type p53 induced phophatase 1), is induced by p53 specifically when in contact with UV radiation, and also by other means when different DNA damage occurs.

This target gene was specifically discussed in two different systems of DNA repair in my articles, *Homeostatic Regulation of Base Excision Repair by a p53-induced phosphotase*, and *Dephosphorylation of γH2AX by WIP1 An important homeostatic regulatory event in DNA repair and cell cycle control*. One system described in *Homeostatic Regulation of Base Excision Repair by a p53-induced phosphotase* was the base excision repair (BER) system. In this system the *PPM1D (*protein phosphatase, Mg2+/Mn2+ dependent, 1D) target gene is upregulated by p53 protein, which in turn produces PPM1D protein. PPM1D significance in the BER repair system is due to its negative feedback activity. During the repair cycle DNA damage activates kinase pathways that can phosphorylate and activate the p53 protein. Along with other processes the p53 protein is active during the repair of DNA, however, how do we stop the cycle once repair is complete? The MAP (mitogen activated protein) kinase pathway is initiated following DNA damage along with other kinase responses. This specific MAP pathway can phosphorylize the p38 protein. This is significant because the p38 protein, when phosphorylated, can increase p53 induced transcriptional regulation as well as cell apoptosis. After the damage is repaired, the p53 protein transactivates the *PPM1D gene* and thus produces PPM1D. PPM1D directly dephosphorylates the p38 map kinase protein, therefore slowing down p53 phosphorylation and ultimately the cell repair cycle. PPM1D slows down the repair cycle by dephosphorylization not only of p53, but also in the enzyme UNG2, linking upstream DNA damage signaling to downstream effectors of DNA repair.

PPM1D's role as a homeostatic mediator was also observed in the article *Dephosphorylation of γH2AX by WIP1 An important homeostatic regulatory event in DNA repair and cell cycle control*. In this paper PPM1D is referred to as WIP1. Although their names may look different, their active role in maintaining homeostasis is similar. The DNA damage researched is a DNA double strand break (DSB). This type of lesion is repaired by the DNA damage response (DDR). After a DSB, protein kinases phosphorylate target proteins such as H2AX, that in turn form docking sites for the MDC1 (mediator of DNA damage checkpoint 1). Recruitment MDC1 activates cell cycle checkpoints that lead to DNA repair. WIP1 directly serves to dephosphorylate γH2AX at a rate of migration that is related to the amount of MDC1 present. Once H2AX is removed of its phosphate groups, the cell repair cycle begins to arrest and yet again, WIP1's role as a homeostatic regulator is shown. Genes such as WIP1 that induce or suppress the cell repair cycle have also been researched in recent years.

In the attempt to make correlation between specific DNA repair genes, scientists who did research for the article, *Differential regulation of expression of the mammalian DNA repair genes by growth stimulation*, tested the regulation of gene expression in two different repair mechanisms, MMR and HMR. By testing to see which genes were growth regulated, they were able to identify differential requirements of the repair genes themselves for example, growth stimulation. In the report, it was tested to see whether or not the mammalian *MSH2, MSH3, MLH1, Rad51,* and *Rad50* genes specifically responded to growth stimulation. It is known that *MSH2, MSH3, and MLH1* genes are a part of the MMR while *Rad50 and Rad51* belongs to the HMR. While testing whether or not growth stimulation play a role in these genes, researchers were led to uncover that growth stimulation played a major role in the positive expression of *MSH2, MLH1, and Rad51.*

On the other hand, the genes *MSH3 and Rad50* showed a low response level to growth stimulation serum. This provides evidence that *Rad50* and *MSH3* are not induced by serum injection. The E2F protein is typically found in gene regulation of DNA replication and codes regularly for transcription factors; however, it also regulates specific repair genes as well. This provides the

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possibility that the DNA repair and replication machineries are closely linked by E2F, which would indicate associations with DNA repair machineries with regard to gene expression that is growth regulated. This protein is able to regulate such mechanisms after it is phosphorylized by the protein kinase ATM. The specific genes tested for their responses to growth stimulation were also observed in their relationship to E2F. Although its presence in other systems of DNA repair affects specific genes, MLH1 and Rad51 promoter activity was not subjected to E2F activation. This suggests that after DNA damage, E2F protein accumulation is not involved in these promoters' regulation. An interesting side note is that the E2F protein also serves as an activator of the p53 protein, which was discussed earlier in *Homeostatic Regulation of Base Excision Repair by a p53-induced phosphotase*.

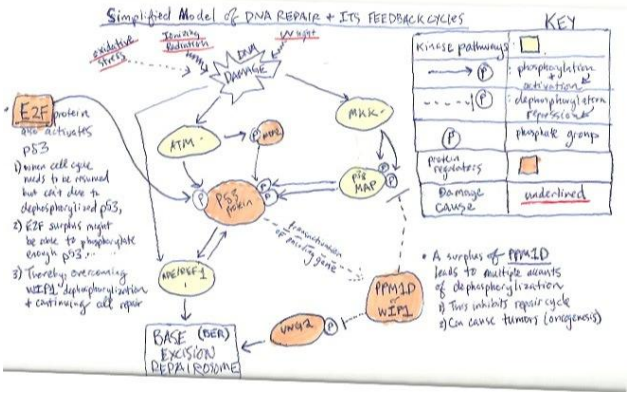

Figure 1

Discussion

After reading through these articles on DNA repair, the complexity of the entire system was made much more exciting when I was able to observe the balanced relationship between many proteins and other regulators of DNA. For example, the negative feedback that the WIP1 (PPM1D) protein exhibits is displayed in the two repair processes of the BER and DDR mechanism for DNA double strand lesions. The WIP1 protein's ability to return the DNA repair cycle to proliferation and continued cell growth its one of the many examples of our bodies use of downstream regulators that act on upstream positive feedback cycles such as the p53 protein. The third article discussed in this review also can be related to this subject in its discussion on growth stimulation affects on DNA replication. Although its activated genes (*MSH2, MSH3, MLH1, Rad51,* and *Rad50*) were different than those in the first two articles (PPM1D a.k.a. WIP1), they were still observed to act on similar protein, p53, however, by alternate means. The growth stimulated genes, *MLH1, and Rad51,* in *Differential regulation of expression of the mammalian DNA repair genes by growth stimulation* were demonstrated to be mediated by the protein E2F. E2F simultaneously serves as a promoter of DNA replication genes as well as a activator of the DNA repair protein p53.

This leads me to draw a possible correlation between replication or growth stimulation, and repair mechanisms. In the event of an upregulation of the *WIP1* gene, it is possible that too much negative feedback prevents the cell repair cycle to fully fix the broken DNA, which can lead to replication of oncogenic cells and cancer. Could additional growth stimulation of E2F activate enough p53 protein to overcome the cancerous effect of over expressed WIP1 protein be the solution to restoring balance in malfunctioning repair cycles? Could specific genes that stimulate the ATM protein kinase directly promote p53 and E2F upregulation and also result in a recovery from over expressed negative feedback proteins? These questions draw a relationship between growth stimulation and repair mechanisms that could be further tested which may lead to alternate pathways that ensure cell repair and growth. As a whole, the DNA repair process is continuously discovered to be complex and interrelated, and by testing and researching the specific regulators of the repair process we can have a deeper understanding its systems and how to mediate them medically. Cancer research on oncogenic cells and how they form can benefit greatly from research articles such as these. The continued importance to test our DNA replication system is imperative in getting us one step closer to understanding our body's complex processes.

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