

UVB Induced Mutation of p53 in Non Melanoma Skin Cancer

Raizy Berger

Raizy Berger graduated June 2018 with a B.S. degree in Biology and is currently attending the Physician Assistant Program at Touro College Manhattan.

Abstract

There is a clear correlation between excessive sun exposure and the development of skin cancer. UVB radiation from the sun is potent, and as the ozone layer gets depleted, more UVB can reach Earth and cause cell damage. UV radiation causes DNA lesions, such as 6-4 photoproducts and cyclobutane pyrimidine dimers. Cyclobutane pyrimidine dimers are more abundant and take longer to be repaired and therefore are responsible for most of the mutation and DNA damage. These DNA lesions lead to mutation of the p53 gene. The signature mutation on p53 from UV radiation is a CC to TT mutation, which generally occurs at the binding site of p53. As a result, of the mutation, p53 is inactivated and can no longer perform its tumor suppressive functions. As a result, cancerous or damaged cells in the skin can proliferate and form tumors. P53 is an early step in skin carcinogenesis, and p53 mutation is found in abundance in actinic keratosis, a precancerous lesion of Squamous Cell Carcinoma. Experiments conducted on mice prove the effectiveness of sunscreen. Mice treated with UVB blocking sunscreen had significantly decreased percentage of mutation, compared to mice without the sunscreen.

Introduction

When summer comes around, it is quite challenging to find a place to sit at the beach. The sands are covered with people sunbathing and basking in the sunlight. Although it is widely known that excessive sun exposure directly correlates to the onset of skin cancer, many people feel that they are immune to the sun's harmful rays and therefore will not develop skin cancer. However, this is not the case, and as they lie there, in denial of the harmful effects of the sun's radiation, they are hurting their bodies. Tanning may cause a more appealing appearance, but in just a few years the harmful effects can emerge and cause a quite dangerous condition, long after the beauty wears away. Sitting directly in the sun, especially without sunscreen, is understandably harmful, but what many people do not realize is that even in cloudy weather eighty percent of the sun's rays can penetrate through the clouds and can still affect the skin (Bowes, 2012). No matter the weather, spending too much time outdoors without the proper protection is detrimental to a person's skin.

In the United States alone there are approximately 500,000 cases of basal cell carcinoma (BCC) and 100,000 to 150,000 cases of squamous cell carcinoma (SCC) reported every year (Kanjilal et al., 1995). Sun exposure proves to be the major factor in the formation of these cancers. Melanoma generally is caused by short incidents of high intensity ultraviolet (UV) radiation. On the other hand, BCC and SCC, known as the non-melanoma skin cancers (NMSC) are generally caused by incidents of exposure to UV radiation which gradually build up. Since NMSC is a result of the collective UV radiation absorption, it is more commonly found in older people (Armstrong and Cust, 2017). Generally skin cancer is more prevalent among fair skinned people, who have less melanin, pigment, which acts as a barrier to UV radiation. Moreover, people who live close to the equator are also at a greater risk for solar UV induced skin cancer, as the sun's rays hit Earth most directly at equator.

No matter the skin tone, too much sun exposure can lead to various issues, such as inflammation, photoaging, erythema, sunburn, eye damage, DNA damage and skin cancer (Benjamin et al., 2007). UV radiation causes damage to DNA, specifically on the p53 gene, a gene with tumor suppressive functions. Once

this gene is mutated, it can no longer act as an anti-oncogene, and cancerous skin cells can metastasize.

Methods

The research discussed in this paper was obtained from various published articles from the Touro Library and Google Scholar. Most of the articles present original information from studies and experiments of tissue and DNA

Discussion: Ultraviolet Radiation

The electromagnetic spectrum is a range of all forms of light, based in their frequency and wavelength. Visible light has wavelengths between 400 and 750 nanometers. UV radiation has shorter wavelengths and therefore higher frequency than visible light. Wavelengths of UV rays are 100 to 400 nanometers (US EPA, 2018). UV radiation is divided into 3 categories, UVA, UVB, and UVC. UVA has wavelengths between 320 to 400 nanometers, and can penetrate through the ozone layer, a protective layer of gas that surrounds earth and protects from harmful UV rays. UVB ranges from 290 to 320 nanometers, and is mostly blocked by the ozone layer, but some rays do come through the ozone and reach Earth. UVC ranges from 100 to 290 nanometers, and is almost entirely blocked by the ozone (Chouinard et al., 2001).

Although UVB is mostly blocked by the ozone, as the stratospheric ozone layer is depleted, UV radiation is more potent and can raise the instances of skin cancer (Nakazawa et al., 1994). UVB has been proven to be the major factor to induce DNA damage, because that specific wavelength can be absorbed by the nucleotide bases that make up DNA (Ichihashi et al., 2003). Wavelengths below 290 nanometers usually get absorbed on the surface of the epidermis, and thus do not cause BCC and SCC (Radosevich, 2014).

Only ten percent of sunlight is UV radiation, as the rest comes from visible and infrared light. Of the ten percent, ninety five percent of it is UVA radiation, and only five percent is UVB (Bowes, 2012). A little bit of UVB is essential for the production of Vitamin D, however, excessive exposure to it can cause erythema, cataracts, or skin cancer (Radosevich, 2014). Even small amounts of UVB exposure can be dangerous if there are

Raizy Berger

repeated incidents, as it will affect the cell formation in the skin by attenuating the basement membrane structure (Chouinard et al., 2001). The weakened membrane allows the UV radiation to reach a person's DNA, specifically that of the p53 gene, a gene with tumor suppressive functions. Once this gene is mutated, it can no longer act as an anti-oncogene.

Function of p53

The p53 protein is made from a 20 Kb gene on the short arm of chromosome 17, which codes for a phosphoprotein involved in transcription and regulation in the cell cycle (Benjamin and Ananthaswamy, 2007). It has been dubbed the name "the guardian of the genome" and "the cellular gatekeeper" (Zilfou and Lowe, 2009). P53 is known this way because of its tumor suppressive functions. P53 gets activated via phosphorylation at a serine residue, at either the amino or carboxyl terminus (Benjamin et al., 2007). Then, it can inhibit the growth of cancerous causing cell cycle arrest, apoptosis, and DNA repair (Ouhit et al., 1998). Cell cycle arrest gives the cell the opportunity to correct DNA complications before the DNA gets replicated. Since the cell is not continuing mitosis at that point, no new cells will be formed with the incorrect DNA. On the other hand, when p53 causes apoptosis, the cancerous cell gets killed and destroyed, and therefore cannot proliferate and become a cancerous growth (Benjamin et al., 2007). Moreover, it can preserve the correct form of the DNA (Einspahr et al., 1999). This is accomplished by "negative growth regulation," which essentially means that p53 stops cell division and proliferation of cells with abnormal DNA (Benjamin and Ananthaswamy, 2007).

Mutation of p53 is usually a missense mutation, a mutation which switches nucleotide in the DNA sequence. Therefore, the codon in the DNA will code for a different amino acid. Such a change affects the protein's function if the mutation results in an amino acid change in the binding site of the protein, which is the case in the p53 missense mutations (Einspahr et al., 1999).

When p53 is mutated it loses its ability to act as an anti-oncogene and suppress tumors, so growth of tumors are then able to grow and form. Tumorigenesis gets inhibited when p53 binds DNA and triggers a different gene to make p21. Once p21 is made, it reacts with a cell division stimulating protein (cdk2), and forms a complex with it. As a result, cdk2 is inactivated and the cell cannot continue with cell division. By stopping cell division, the cells cannot multiply and grow to form a tumor. However, when p53 gets mutated, it can no longer interact with DNA the same way, so p21 is not produced, cdk2 is not inhibited and cancerous cells can continue multiplying and form a tumor (National Center for Biotechnology Information (US), 1998).

UV Damage Adducts: Cyclobutane Pyrimidine dimers and 6-4 Photoproducts

BCC and SCC are mainly caused by UV radiation (You et al., 2001).

Studies have shown that 58% of SCC has a mutation on the p53 gene (Benjamin et al., 2007). UVB specifically causes bulky linkages between pyrimidine dimers (Sarasin and Giglia-Mari, 2002). DNA is made up of nucleic acid, which is a linear polymer of nucleotides. Each nucleotide contains a ribose sugar, phosphate group and a nitrogen base. There are four different nitrogen bases found in DNA: adenine, guanine, cytosine and thymine. Adenine and guanine have similar ring structures and are classified as purines. Cytosine (C) and thymine (T) have a similar ring structure (different than that of the purines) and are classified as pyrimidines. A pyrimidine dimer can form when two pyrimidine nucleotides are adjacent to each other on a DNA strand.

These pyrimidine dimer linkages can mainly be corrected by nucleotide excision repair. (Sarasin and Giglia-Mari, 2002). Nucleotide excision repair can repair UV induced pyrimidine dimer linkages before DNA replication, or after replication by using a specific DNA polymerase which corrects DNA. The repair process begins with recognizing the damage on the DNA. The DNA is then cut on either side of the lesion on a single strand of DNA, and the damaged area is extracted. Next, the removed segment is replaced with new nucleotides to recreate the DNA properly. The process is complete when ligation occurs, and the newly formed DNA segment is linked to rest of the strand. Two approaches to nucleotide excision repair are transcription coupled repair, which is done on DNA strands that are actively transcribed, and global genome repair which occurs on the non-transcribed strand of DNA. Transcription coupled repair requires is generally faster than global genome repair in DNA repair (de Gruijl and Rebel, 2008). Global genome repair deals with damage recognition and correction of pyrimidine dimer linkages. The damage recognition stage takes some time, depending on the effect of the damage on the structure of the DNA helix, and is the rate limiting aspect in repair, which makes global genome repair slower than transcription coupled repair (Ichihashi et al., 2003). The significance of nucleotide excision repair can be understood by studying patients with Xeroderma Pigmentosum, a genetic disease in which DNA repair from UV radiation, nucleotide excision repair, is impaired. Individuals with this disorder have a much higher rate of developing skin cancer, since they have more uncorrected pyrimidine dimer linkages that lead to mutation (de Gruijl and Rebel, 2008). Early growth of skin cancer is noted in Xeroderma Pigmentosum patients with a frequency of approximately 4000 more than regular people (Sarasin and Giglia-Mari, 2002).

UVB can cause two types of DNA lesions on the p53 protein, cyclobutane pyrimidine dimers (CPD) and pyrimidine 6-4 pyrimidone photoproducts (6-4PP). Both of these linkages lead to C to T or CC to TT mutations, known as "signature mutations," on gene p53 in DNA (You et al., 2001). In a study of tissue with different levels of sun exposure and sun damage, it was noted that 74% of the mutation of p53 occurred at dipyrimidine sites, and

UVB Induced Mutation of p53 in Non Melanoma Skin Cancer

54% were C to T, or CC to TT mutations (Einspahr et al., 1999).

CPDs are the cause of 80% of the DNA mutations, since 6-4 PP can be repaired more efficiently (You et al., 2001). The repair of 6-4 PP can occur within less than 24 hours of the UV exposure (de Gruijl and Rebel, 2008). In fact, 56% of keratinocytes corrected the 6-4 PP within 24 hours. Conversely, only 11% of CPDs were remedied within the first 24 hours after UVB exposure (Chouinard et al., 2001). CPDs are less effectively repaired and can lead to mutation of p53 and then skin cancer. Moreover, there are generally CPDs are 3 to 4 times more commonly formed than 6-4 PP (de Gruijl and Rebel, 2008). Experimentally it has been observed that 6-4 PP were formed significantly less often than CPD overall, and even more rare in experiments with solar UV simulation. Therefore, in natural sunlight, 6-4 PP are found at a much lower percentage than CPDs (You et al., 2001).

UVB from sunlight will cause CPD formation, especially at pyrimidine dimers which have methylated cytosine nucleotides (You, 2000). A CCG sequence with a methylated cytosine is a common place for mutation, since a methylated cytosine is less stable than regular cytosine and can be deaminated easily. The deamination of a methyl cytosine yields a thymine nucleotide, a DNA mutation (Sarasin and Giglia-Mari, 2002). CPDs only can cause mutations to develop after the deamination of a methyl-cytosine in adduct (You et al., 2001). The CCG sequence codes for the amino acid arginine, and when the cytosine nucleotide gets converted to thymine, the sequence now codes for tryptophan. This switch of amino acids is extremely important to the p53 gene since that arginine is found at p53's binding site (Sarasin and Giglia-Mari, 2002). Since arginine and tryptophan have different side chains they react differently and thus will affect the binding of p53 to the target DNA. Arginine contains a second amino group on its side chain, which can act as a base and get protonated. Tryptophan side chain is two fused aromatic rings, and the nitrogen in its side chain is an extremely weak base, as it loses its aromaticity when protonated. Therefore, mutation and transition of the nucleotide at this sequence greatly affects the function and capabilities of p53.

Mutation of p53 and Carcinogenesis

Genetic mutations of p53 have clear correlations with the growth of cancer. When p53 is inactivated or mutated, the skin becomes more vulnerable to carcinogenesis (de Gruijl and Rebel, 2008). UV radiation provokes the growth of skin tumors, mostly SCC and BCC (You et al., 2001). Basal cells are on the bottom layer of the epidermis and rise slowly as new layers grow beneath them. As a result, these cells stay in the epidermis the longest, until the rise from the bottom layer until they eventually reach the top and die. Therefore UV damage to these cells has a long term capability to cause cancer, since they are in the skin for the longest time (de Gruijl, 2002).

P53 mutation is found in about 50% of all types of cancer. UV

radiation causes specific mutations in p53 which can result in skin cancer. It causes cancerous growths by stimulating different growth factors and activating their receptors. Moreover, each instance of UV exposure helps mutated cells reproduce and take over healthy epidermal cells, even if it does not induce new mutations. Although the cell has protective mechanisms against DNA mutation, UV sometimes can still cause DNA damage. Buildup of mutations on critical genes leads to carcinogenesis of the skin. Many mutations of p53 are even noted in normal looking skin which has been exposed to the sun (Benjamin and Ananthaswamy, 2007). Most of the mutations found in p53 in people with skin cancer, prove to have UV radiation as the cause. Once p53 is mutated, it affects the availability for apoptosis to occur in keratinocytes, as a response to UV radiation. Apoptosis is a programmed cell death. In tissues that are constantly renewing, apoptosis is involved in homeostasis, as more cells are reproducing, others are destroyed through apoptosis. When a gene which deals with apoptosis is mutated, it can result in too much growth, since cells are not dying as new cells are being formed. Moreover, p53 maintains "genomic integrity" by repairing the DNA or causing apoptosis in a cell with mutant DNA. However, when p53 is mutated, it can no longer function in this way. In cancer, generally the mutation of p53 occurs further into the tumorigenic process. In contrast, in NMSC the mutation in p53 is an early step in carcinogenesis (Einspahr et al., 1999).

Mutated cells have overexpression of the p53 protein and form "p53 patches." Most p53 patches had signature UVB damage. The mutation spectrum observed is quite similar to the mutation spectrum of SCC. As a result of the damage, the functions of p53, like apoptosis and cell cycle arrest, are interrupted. Since these processes generally occur to prevent cancerous growth, UV induced damage which impacts them likely occurs early in cancer development. Although all p53 have the potential to become SCC, only a few do actually become cancerous. Approximately 8000 to 40000 p53 patches are around by the time the first tumorous growth begins (de Gruijl and Rebel, 2008).

UV induced mutations in p53 most likely occur as an early step in the process of skin carcinogenesis. However in other cancers, like colon cancer p53 mutations generally occur later in the development of the cancer, particularly related to the change from an adenoma to a carcinoma (Benjamin and Ananthaswamy, 2007). This phase of cancer is much later in the development as cancer progresses from normal epithelium, to abnormal epithelium, to a small adenoma, to larger adenoma, and finally to a carcinoma.

Actinic keratosis (AK) is a precancerous lesion which can lead to SCC. The frequency of a p53 mutation has been studied with different conditions of skin. In a particular study, the frequency of a p53 mutation in SCC was 53.8%, in AK it was 62.5%, in sun damaged skin it was 38.5%, and in normal skin it was 14.3%. The mutation is observed to have a higher frequency in skin

from an AK lesion. This could be because the tissue samples obtained from AK lesions are closer to the surface of the skin, and the tissue samples of SCC are deeper in the skin and could be contaminated from the stromal tissue (Einspahr et al., 1999).

Approximately 89% of the mutations found in AK, were UV signature mutations. Therefore, it is believed that AK is the growth of mutated, cancerous cells. Moreover, the UV does not only cause great increase in reproduction of the mutated cells, but also causes apoptosis of normal cells in the area of hyperproliferation (Benjamin and Ananthaswamy, 2007). Various studies of skin have found a lot of p53 mutations in BCC and SCC. Samples of 342 tissues from patients with aggressive and non-aggressive cases of SCC and BCC were studied for p53 changes. In BCC, 66% of the aggressive cases and 38% of the non-aggressive cases had p53 changes. In SCC, p53 mutations were observed in 35% of the aggressive cases and 50% of non-aggressive cases (Benjamin and Ananthaswamy, 2007).

In a study of eight samples of NMSC, from the head and neck, 7 of the samples (88%) had p53 mutation. Six of the tissues had at least two amino acid changes as a result of the mutation, which were mainly at the binding site of p53 (Kanjlil et al., 1995).

In Approximately 38-50% of patients with NMSC, a second tumor grows within five years of the first one. A patient with skin cancer needs a lot of medical intervention, surgical procedures, and sometimes radiotherapy (Kanjlil et al., 1995).

Prevention

Since NMSC can be caused by UVB from sunlight, protection from the sun's powerful rays would be a great means of prevention. DNA damage and mutation of p53 are the beginning steps of the development of skin cancer; by preventing them skin cancer can be prevented as well (El-Deiry, 2007). Sunscreen can effectively protect the skin from UV induced DNA damage and p53 mutation, since it can absorb or reflect the harmful UV rays so they do not penetrate the cells (Radosevich, 2014). Sunscreens have been proven to protect against DNA damage, skin aging, sunburn, immunosuppression, and skin carcinogenesis. Although it can be obviously observed that sunscreen prevents erythema and sunburn, experiments and studies must be conducted to see if it is useful in preventing deeper damage, like p53 mutation (Benjamin et al., 2007).

The effectiveness of sunscreen in preventing mutations, can be proven based on a murine experiment. After conducting experiments to prove that UV radiation causes p53 mutation, another experiment was conducted to understand if sunscreen can prevent the p53 mutations from happening. Both sunscreens used in this experiment had an SPF (sunburn protection factor) of 15. One sunscreen had only UVB protection, and the other had protection for UVB as well as protection from UVA. The mice who had the UVB sunscreen, developed p53 mutations 88% less than mice without sun protection, and those with UVB

+UVA sunscreen had 92% less mutations. Therefore, this experiment clearly displayed the capability of sunscreen to inhibit p53 mutation. Since p53 mutation is an integral step in carcinogenesis, if mutation is prevented, skin cancer is less likely to develop (Ananthaswamy, Ullrich and Kripke, 2002).

Another strategic tactic to avoid or delay carcinogenesis is to minimize sun exposure. Some UV exposure is necessary for the body, as it plays an important role in the synthesis of vitamin D, excess exposure can cause skin cancer (Radosevich, 2014). Studies have proven that p53 patches grow more when exposed to additional UV exposure. Although reducing UV exposure cannot eliminate the possibility of skin cancer, it can delay its progression and development (Benjamin et al., 2007).

The Environmental Protection Agency (EPA) notes that at noon the sun's rays are most powerful as they travel the least distance to reach Earth. Therefore, it would be wise to avoid unnecessary UV exposure at that time. The EPA also recommends applying sunscreen, seeking shade when possible, keeping aware the UV index, and being exceptionally cautious around areas that can reflect the sun's rays, such as water, snow, and sand (US EPA, 2018).

Conclusion

UVB induced mutation of p53 leads to the development of skin cancer. UV radiation causes the formation of pyrimidine dimers on the p53 protein. P53 is an anti-oncogene, which prevents tumorigenesis by causing cell cycle arrest or apoptosis. When p53 is damaged by UV mutation it can longer function and cancerous basal and squamous cells can proliferate and grow. Cancerous areas show overexpression of p53 and are referred to as "p53 patches." These patches will grow more when exposed to more UV radiation, even if the radiation will not cause a new mutation to form in that instance. Sunscreen usage and minimization of sun exposure are affective approaches to prevent UV damage of p53 and skin carcinogenesis.

References

- Ananthaswamy, H., Ullrich, S. and Kripke, M. (2002). Inhibition of UV-induced p53 mutations and skin cancers by sunscreens: implication for skin cancer prevention. *Experimental Dermatology*, 11(s1), pp.40-43.
- Armstrong, B. and Cust, A. (2017). Sun exposure and skin cancer; and the puzzle of cutaneous melanoma. *Cancer Epidemiology*, 48, pp.147-156.
- Benjamin, C. and Ananthaswamy, H. (2007). p53 and the pathogenesis of skin cancer. *Toxicology and Applied Pharmacology*, 224(3), pp.241-248.
- Benjamin, C., Ullrich, S., Kripke, M. and Ananthaswamy, H. (2007). p53 Tumor Suppressor Gene: A Critical Molecular Target for UV Induction and Prevention of Skin Cancer. *Photochemistry and Photobiology*, p.071027164408001
- Bowes, L. (2012). Understanding the dermal effects of

UVB Induced Mutation of p53 in Non Melanoma Skin Cancer

- heightened exposure to the sun. *Journal of Aesthetic Nursing*, 1(1), pp.25-31.
- Chouinard, N., Therrien, J., Mitchell, D., Robert, M., Drouin, R. and Rouabhia, M. (2001). Repeated exposures of human skin equivalent to low doses of ultraviolet-B radiation lead to changes in cellular functions and accumulation of cyclobutane pyrimidine dimers. *Biochemistry and Cell Biology*, 79(4), pp.507-515.
- de Gruijl, F. (2002). p53 mutations as a marker of skin cancer risk: comparison of UVA and UVB effects. *Experimental Dermatology*, 11(s1), pp.37-39.
- de Gruijl, F. and Rebel, H. (2008). Early Events in UV Carcinogenesis—DNA Damage, Target Cells and Mutant p53 Foci. *Photochemistry and Photobiology*, 84(2), pp.382-387.
- Einspahr, J., Alberts, D., Wameke, J., Bozzo, P., Basye, J., Grogan, T., Nelson, M. and Bowden, G. (1999). Relationship of p53 Mutations to Epidermal Cell Proliferation and Apoptosis in Human UV-Induced Skin Carcinogenesis. *Neoplasia*, 1(5), pp.468-475.
- El-Deiry, W. (2007). Targeting mutant p53 shows promise for sunscreens and skin cancer. *Journal of Clinical Investigation*, 117(12), pp.3658-3660.
- Ichihashi, M., Ueda, M., Budiyo, A., Bito, T., Oka, M., Fukunaga, M., Tsuru, K. and Horikawa, T. (2003). UV-induced skin damage. *Toxicology*, 189(1-2), pp.21-39.
- Kanjilal, S., Strom, S. S., Clayman, G. L., Weber, R. S., el-Naggar, A. K., Kapur, V., Kripke, M. L. (1995). p53 mutations in nonmelanoma skin cancer of the head and neck: Molecular evidence for field cancerization. *Cancer Research*, 55(16), 3604.
- Nakazawa, H., English, D., Randell, P., Nakazawa, K., Martel, N., Armstrong, B. and Yamasaki, H. (1994). UV and skin cancer: specific p53 gene mutation in normal skin as a biologically relevant exposure measurement. *Proceedings of the National Academy of Sciences*, 91(1), pp.360-364.
- National Center for Biotechnology Information (US). (1998, January 01). The p53 tumor suppressor protein. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK22268/>
- Nelson, D., Cox, M. and Lehninger, A. (2013). *Lehninger principles of biochemistry*. New York: W.H. Freeman and Company.
- Ouhtit, A., Nakazawa, H., Yamasaki, H., Armstrong, B., Krickler, A., Tan, E. and English, D. (1998). UV-Radiation-Specific p53 Mutation Frequency in Normal Skin as a Predictor of Risk of Basal Cell Carcinoma. *JNCI: Journal of the National Cancer Institute*, 90(7), pp.523-531.
- Radosevich, J. A. (2014). *UV Radiation : Properties, Effects, and Applications*. New York: Nova Science Publishers, Inc.
- Sarasin, A. and Giglia-Mari, G. (2002). p53 gene mutations in human skin cancers. *Experimental Dermatology*, 11(s1), pp.44-47.
- US EPA. (2018). UV Radiation | US EPA. [online] Available at: <https://www.epa.gov/sunsafety/uv-radiation-1>
- You, Y. (2000). Cyclobutane pyrimidine dimers form preferentially at the major p53 mutational hotspot in UVB-induced mouse skin tumors. *Carcinogenesis*, 21(11), pp.2113-2117.
- You, Y., Lee, D., Yoon, J., Nakajima, S., Yasui, A. and Pfeifer, G. (2001). Cyclobutane Pyrimidine Dimers Are Responsible for the Vast Majority of Mutations Induced by UVB Irradiation in Mammalian Cells. *Journal of Biological Chemistry*, 276(48), pp.44688-44694.
- Zilfou, J. and Lowe, S. (2009). Tumor Suppressive Functions of p53. *Cold Spring Harbor Perspectives in Biology*, 1(5), pp.a001883-a001883.