Chapter 21

The Molecular Epidemiology of DNA Repair Polymorphisms in Carcinogenesis

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Additional information is available at the end of the chapter

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1. Introduction

There are well-established examples of highly penetrant mutations in genes that are directly involved in carcinogenesis and result in a high risk of cancer in the individuals who carry these mutations. Some of the best examples include syndromes of defective DNA repair, such as xeroderma pigmentosum [1]. However, these examples tend to be very rare and thus contribute minimally to the overall burden of cancer risk. Nevertheless, it has long been suspected that less penetrant susceptibility may be produced by much more common variants in the same cancer-related genes, for example, in the form of single nucleotide polymorphisms (SNPs), that presumably would be less disruptive and therefore produce more subtle effects on the function of the encoded proteins but which could contribute greatly to overall cancer attributable risk in populations due to their widespread occurrence [1]. Because several of these common polymorphisms occur in DNA repair proteins, many epidemiologic studies have examined their relationship to cancer risk [2-4].

These studies have looked at all different types of cancer, many different at-risk populations, several different DNA repair pathways, and a variety of polymorphisms at different sites [5-18]. The results to date at best have been inconsistent, conflicting and confusing with many examples of positive, negative or null associations between particular polymorphisms and particular cancers, even in multiple large meta-analyses of the data. For example, a very recent large, rigorous and systematic review of the literature on the involvement of DNA repair polymorphisms in human cancer reached the conclusion that because of the inconsistencies in the literature "none of the cancer genome-wide association studies (GWAs) published so far showed highly statistically significant associations for any of the common DNA repair gene variants" and "clarification of the discrepancies in the literature is needed." [4] It was suggested

that one way to proceed would be that "gene/environment and gene/lifestyle interactions for carcinogenic mechanisms involving DNA repair should be investigated more systematically and with less classification error." [4] However, even in studies of populations with exposures to known environmental carcinogens and the cancers most closely associated with those exposures, the results of DNA repair polymorphism studies have not always been clear-cut; these inconsistencies may also be the result of poor exposure classification, multiple confounders and/or poor understanding of the exact mechanisms of DNA damage and/or repair [19-23]. In other words, what is needed is to study model systems where there are clear linkages between the exposure to the carcinogenic risk factor and the specific DNA damage that it produces with the DNA repair mechanisms that would correct those particular defects.

In environmental carcinogenesis studies of DNA repair polymorphisms, the majority of the work has focused on base excision repair (BER) or nucleotide excision repair (NER) pathways, since these are thought to play dominant roles in the repair of damage from exogenous carcinogens, including chemical carcinogens. In both of these pathways, numerous polymorphisms in numerous proteins that make up the DNA repair machinery have been examined. However, much of the focus has been on the particular proteins in the respective pathways that contain the most common polymorphic variants, in particular the x-ray cross complementing-1 (XRCC1) protein in BER and the xeroderma pigmentosum-D (XPD) protein in NER [24-38].

This is also understandable because of the critical roles that each of these proteins play in their respective pathways. For example, in BER the particular type of damage produced by exposure to a chemical carcinogen is usually recognized and removed by a specific DNA glycoslase. The BER apparatus includes numerous other proteins that complete the repair at the resultant abasic site once the damage is removed: apurinic/apyrimidinic endonuclease (APE1), poly(ADP-ribose) polymerase-1 (PARP-1), poly(ADP-ribose) polymerase-2 (PARP-2), DNA polymerase β (Pol β) and DNA ligase IIIα (Lig III). AP endonuclease is responsible for cleaving the phosphodiester bond at the abasic site created by the glycosylase. PARP-1 and to a lesser extent PARP-2 participate in the repair process by catalyzing ribosylation of a number of DNA-bound proteins, thereby decreasing the affinity of these proteins for DNA, and allowing the repair machinery to access the damaged site. Pol β, the polymerase involved in short patch repair, provides two essential activities, deoxyribophosphodiesterase activity which releases the 5' sugar phosphate group, and gap filling synthesis, where one nucleotide is added to the 3' OH. Finally, Lig III seals the nick in an ATP-dependent manner [39, 40]. The XRCC1 protein is critical to this process since it acts as a scaffold protein in this pathway and appears to enhance the activity of the other BER proteins. Although XRCC1 has not been demonstrated to contain enzymatic activity of its own, it is thus necessary for coordinating and regulating the early and late stages of BER through its protein interaction modules [41, 42].

XRCC1 is known to contain three common polymorphic sites that might be expected to have an effect on XRCC1 structure and function because they occur in or near important protein domains [11]. For example, the polymorphism at amino acid residue 194, which results in the substitution of a tryptophan for the normal arginine, occurs in the XRCC1 N-terminal domain from amino acid residues 1-195 that has been observed to mediate its interaction with the palm-

thumb domain of Pol β [43]. A second polymorphism at amino acid residue 280, which results in the substitution of a histidine for the normal arginine, occurs in the region between the N-terminal domain and the BRCA1 carboxy terminal (BRCT1) domain of the protein and close to the nuclear localization signal site and thus could affect the relationship between these two critical domains and/or the protein's localization ability [44]. The third and most common polymorphism in XRCC1 occurs at amino acid residue 399, resulting in the substitution of a glutamine for the normal arginine, within the highly conserved BRCT1 domain from amino acid residues 315-403, which has been associated with the functioning of PARP1, PARP2 and APE1 [45].

Like BER, NER occurs in a series of steps: damage recognition, unwinding and demarcation of the DNA, excision of the single-stranded fragment containing the damaged site, and DNA re-synthesis. NER is accomplished primarily through the action of proteins of the xeroderma pigmentosum family of genes which are categorized into 7 different groups (A-G). XPC and XPE proteins are involved in recognition of different types of DNA damage. XPB and XPD are DNA helicases that function as subunits of the transcription factor IIH complex (TFIIH) to promote DNA bubble formation at the damaged site by unwinding the DNA as XPA complexes with replication protein A (RPA) for demarcation. XPF and XPG are structure-specific endonucleases for excision of the damaged site. Finally, replicative DNA polymerase and DNA ligase I complete the repair [46, 47]. XPD is one of the major players in NER and is essential for life [48, 49].

XPD is also known to contain at least two common polymorphic sites, namely at amino acid residues 312 (aspartic acid->asparagine) and 751 (lysine->glutamine) [50]. The 751 site is assumed to be particularly important for XPD function since it occurs in the C-terminal domain of the protein which has been suggested to interact with the p44 helicase activator protein of the TFIIH complex [51]; also, it is been shown that an XPD mutation that results in the loss of the final 17 C-terminal amino acids, including residue 751, results in the clinical disease phenotype of trichothiodystrophy [52].

In summary, an ideal system for investigating the role of DNA repair polymorphisms in carcinogenesis might be an exposure to a known chemical carcinogen that produces specific types of DNA damage that are repaired by the BER and/or NER pathways where the effects of common polymorphisms in XRCC1 and XPD on the damage and repair could be studied.

2. A model for the study of the epidemiology of dna repair polymorphisms in carcinogenesis

Such a potential model system for the study of the role of DNA repair polymorphisms in chemical carcinogenesis is provided by the known carcinogen vinyl chloride (VC) because considerable detail is available concerning the molecular biology of its pathogenic pathway which allows for careful study of the role of DNA damage and repair in the carcinogenic process in exposed human populations through the application of molecular epidemiologic approaches (Figure 1).

As noted, VC is a well-established animal and human carcinogen. It is most strongly associated with liver cancer, in particular the rare, sentinel neoplasm of angiosarcoma of the liver (ASL), a malignant tumor of the endothelial cells of the liver [53]. However, VC has also been identified as a cause of hepatocellular carcinoma (HCC), the corresponding malignant tumor of the parenchymal cells of the liver [54]. In addition, it has been associated with other malignancies, e.g., lung and brain, although these associations remain much more controversial. The most significant exposures to VC occur in the petrochemical and plastics industries because VC is used in the manufacture of polyvinyl chloride, one of most high-volume plastics in the world. For example, it is estimated that worldwide more than 2,200,000 workers are probably occupationally exposed to VC. General population exposures also occur primarily through the air and water. For example, elevated levels of VC have been found not only in the air near VC manufacturing and processing facilities but also in the vicinity of many hazardous waste sites and municipal landfills, either due to the direct disposal of VC or from the microbial degradation of other chlorinated solvents to form VC. In some cases, dangerously high levels have been detected in the air at some of these landfills [53]. General population exposures may also occur from tobacco smoke, drinking water from PVC pipe, and consumption of food and beverages from PVC packaging and bottles, although probably at much lower levels.

VC is a gas so the most significant exposures are respiratory. Following inhalation, absorption is rapid in humans and most subsequent metabolism occurs in the liver [53]. Phase I metabolism is primarily via the cytochrome P-450 isoenzyme 2E1 (CYP2E1) to generate the reactive intermediates chloroethylene oxide (CEO) and chloracetaldehyde (CAA) which are further metabolized in phase II reactions by glutathione-S-transferases (GSTs) and aldehyde dehydrogenase 2 (ALDH2) to end products for ultimate excretion. However, CEO and CAA can readily interact with cellular macromolecules, including DNA, to produce promutagenic effects. VC biotransformation to CEO probably occurs principally in hepatocytes, but the epoxide can also reach and react with adjacent sinusoidal lining cells, so that mutagenic effects can occur in parenchymal liver cells and non-parenchymal endothelial cells, providing a logical rationale for the association between VC exposure and ASL as well as HCC [55]. The major VC-associated liver DNA adduct is 7-(2-oxoethyl)guanine, comprising up to 98% of all adducts formed. However, this adduct is eliminated from the DNA with a very short half-life, principally by chemical depurination, and is not considered to be promutagenic. On the other hand, three etheno DNA adducts are also formed in much less abundance, but they are known to be promutagenic. These are: N^2,3-ethenoguanine (εG) ; 1,N^6-ethenoadenine (εA) ; and 3,N^4-ethenocytosine (εC) [56].

The promutagenic properties of etheno-DNA adducts that are not fully repaired by one or another of the DNA repair pathways have been well documented in experimental systems *in vitro*, as well as *in vivo* in bacterial and mammalian cells. The εA adduct generates A->T, A->G and A->C base changes; the εG adduct generates G->A base changes; and the εC adduct generates C->A and C->T base changes [55]. These experimental results are consistent with the tumor mutational spectra identified in exposed animals and humans in oncogenes and tumor suppressor genes. Of particular interest have been the A->T transversions at codons 179, 249 and 255 of the *TP53* tumor suppressor gene generated by εA adducts and the G->A transitions

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at codon 13 of the K-*ras* oncogene generated by εG adducts, because of their frequent occurrence in human ASLs from VC-exposed individuals but not in sporadic ASLs in individuals without VC exposure. In addition, other results suggest that these VC-associated mutations, particularly the codon 13 K-*ras* mutation, may be a relatively early event in VC carcinogenesis, and thus the occurrence of these mutations may be useful biomarkers of cancer risk in exposed individuals, as discussed below.

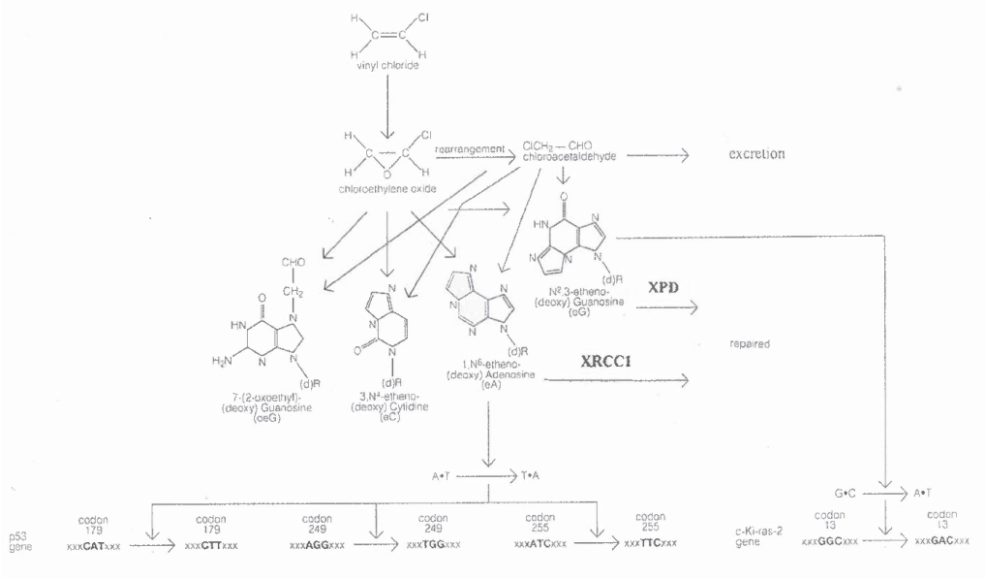

Figure 1. Proposed mechanism of VC-induced DNA damage and repair as a model system for the study of the effects of polymorphisms in BER and NER pathways.

The G->A transition at codon 13 of K-*ras* results in the substitution of an aspartic acid for the normal glycine at amino acid residue 13 in the encoded p21 protein product. This substitution is believed to be oncogenic, having been identified in other human tumors as well. The oncogenic mechanism of action of this substitution is thought to be through the production of a conformational change in p21 which may be responsible for altering its intrinsic GTPase activity, thus affecting signal transduction within the cell leading to uncontrolled growth and division [57]. Similarly, the A->T transversions at various codons of *p53* produce their corresponding amino acid substitutions in the encoded p53 protein product, all changes that have been shown to cause the protein to adopt its so-called "malignant" conformation with a concomitant loss of its normal tumor suppressor activity [57]. These protein changes provide a useful indicator of the pathogenic consequences of the occurrence of the corresponding mutations, as well as convenient intermediate biomarkers of VC effect to study the molecular epidemiology of VC carcinogenesis in exposed human populations, including the effects of polymorphisms in the relevant DNA repair pathways.

It has been shown that the mutant *ras*-p21 protein containing aspartic acid for glycine at amino acid residue 13 can be distinguished from the wild-type protein and other mutant *ras*-p21 proteins immunologically with a mouse monoclonal antibody specific for this protein. For cells in culture that contain the mutant *ras* gene, it is possible to use this monoclonal antibody to detect mutant *ras*-p21 expression in the cells by immunocytochemistry and in the extracellular supernatant by immunoblotting. In analogous situations *in vivo*, mutant Asp 13 *ras*-p21 can be detected in tumor tissue by immunohistochemistry and in the serum by immunoblotting of VC-exposed workers with ASLs known to contain the mutant *ras* gene but not in the serum of VC-exposed workers with ASLs that do not contain the mutation or in unexposed controls [57-59].

An analogous, although slightly more complicated situation occurs with p53. As noted, all of the VC-induced mutations in the *p53* gene have been shown to cause a similar conformational change in the encoded p53 protein that results in the exposure of a common epitope, which is normally not immunologically detectable in the wild-type protein. Thus, these mutant p53 proteins can be distinguished from wild-type p53 immunologically with a mouse monoclonal antibody that binds to this mutant-specific epitope. For cells in culture that contain the mutant *p53* genes, it is possible to use this monoclonal antibody to detect mutant p53 protein expression in the cells by immunocytochemistry and in the extracellular supernatant by immunoblotting or by enzyme-linked immunosorbent assay (ELISA). In the analogous situation *in vivo*, mutant p53 can be detected in the tumor tissue by immunohistochemistry and in the serum by immunoblotting or ELISA of VC-exposed workers with ASLs known to contain the mutant p53 genes but not of VC-exposed workers with ASLs that do not contain the mutations or in unexposed controls. In some cases of mutant p53-positive tumors, it is known that individuals can also develop an antibody response to the mutant p53 which can obscure the detection of the mutant p53 protein itself. However, it is also possible to detect these autoantibodies to mutant p53 using an ELISA. Thus, the detection in serum of mutant p53 protein and/or an antibody response to mutant p53 protein can be used together to best identify individuals who have a *p53* mutation in their tumors [57, 60, 61].

Based on the above evidence, it seems that these serum biomarkers for mutant *ras*-p21 and mutant p53 accurately reflect the occurrence of the corresponding DNA damage in the target tissue of VC-exposed workers. In addition, these biomarkers have been identified not only in VC-exposed workers with ASLs but also in VC-exposed workers with non-malignant (but potentially pre-malignant) angiomatous lesions and in VC-exposed workers without any apparent neoplastic disease [57, 62-64]. In a large cohort of French VC workers, the presence of these biomarkers was found to occur with a highly statistically significant dose-response relationship with regard to estimated, cumulative VC exposure, supporting the claim that the generation of the biomarkers was indeed the result of the exposure [65]. Similar results with these biomarkers have been noted in several other VC workers cohorts around the world [66-71]. To date in these various studies, at least five VC-exposed biomarker-positive workers without ASL have developed subsequent liver lesions presumed to be ASLs, also suggesting that these biomarkers may have predictive value for the subsequent occurrence of cancer.

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However, at any given level of VC exposure, some workers will have none, one or both mutant biomarkers. One possible explanation for this inter-individual variability is genetic differences in the proteins that metabolize VC or repair the DNA damage it produces. Although polymorphisms in the proteins involved in metabolizing VC have been shown to have an effect, polymorphisms in DNA repair proteins have been found to be even more significant.

There are several potential mechanisms by which VC-induced adducts could be repaired before they have a chance to cause mutations. As noted above, the oxoethyl adduct is removed rapidly by chemical depurination. The potential repair of the etheno adducts, however, is more complicated and involves the BER and NER pathways.

For example, the 1,N^6-εA adducts are recognized and removed by 3-methyl adenine DNA glycosylase which is part of the BER pathway [55]. Likewise, the 3,N^4-ethenocytosine adducts are also repaired with high efficiency by BER via the thymine DNA glycosylase. Therefore, polymorphisms in the BER pathway that could decrease DNA repair efficiency, particularly the polymorphisms in XRCC1, might be expected to result in an increase in εA and εC adduct levels at any given level of exposure in VC-exposed individuals with a resultant increase in the VC-associated mutant biomarkers, particularly the mutant p53 biomarker. In contrast, the N^2,3-ethenoguanine adducts have been shown to be not very efficiently repaired by BER [56, 72]. Thus, if they are repaired, it is likely to be by a different DNA repair pathway such as NER. Therefore, polymorphisms in the NER pathway that could decrease DNA repair efficiency, particularly the polymorphisms in XPD, might be expected to result in an increase in εG adduct levels at any given level of exposure in VC-exposed individuals with a resultant increase in the VC-associated mutant biomarkers, particularly the mutant *ras*-p21 biomarker.

In fact in the aforementioned French VC worker cohort, we have been able to identify the effect of the XRCC1 polymorphisms on the occurrence of the mutant p53 biomarker, but not the mutant *ras*-p21 biomarker [73-75]. The difference in effect on the two biomarkers is expected, since, as noted the εA adducts that result in the mutant p53 biomarker are repaired efficiently by BER but the εG adducts that result in the mutant *ras*–p21 biomarker are not, so changes in XRCC1 might affect the former but should not affect the latter. Among the three XRCC1 polymorphisms, the most significant effect on the mutant p53 biomarker was attributable to the residue 399 polymorphism. In this case, individuals who were homozygous variant Gln-Gln at 399 had a statistically significant 1.9-fold risk of occurrence of the mutant p53 biomarker compared to homozygous Arg-Arg wild-type individuals, even after controlling for potential confounders including cumulative VC exposure, and the gene-environment interaction between the polymorphism and VC exposure appeared to be potentially supra-multiplicative [75]. Studies in other VC worker populations have found similar effects of the XRCC1 polymorphisms, particularly the 399 polymorphism, on the mutant p53 biomarker, as well as other biomarkers of DNA damage [76-79].

This is also consistent with various experimental results examining this model system. For example, molecular modeling of the BRCT1 domains of the normal and polymorphic forms of XRCC1 demonstrates that the 399 substitution produces significant conformational changes in this domain, including the loss of secondary structural features such as α-helices that can be critical for mediating protein-protein interactions that would allow XRCC1 to coordinate

BER [80]. Also, studies of lymphoblasts from individuals of different genotypes exposed *in vitro* to the reactive metabolites of VC showed that cells with the XRCC1 399 homozygous variant Gln-Gln genotype had an approximate 4-fold decrease in efficiency of repair of εA DNA adducts compared to cells with the homozygous wild-type Arg-Arg genotype [74, 81], resulting in an approximate 1.8-fold increase in mutation frequency in the polymorphic cells compared to the wild-type cells as determined by the hypoxanthine-guanine phosphoribosyltransferase (HPRT) assay [82]. Based on mutational spectrum studies in CAA-exposed human cell lines [83], the resultant increase in ▪ A DNA adducts would especially result in an increase in A->T transversions consistent with those found in the tumors of VC-exposed workers, as noted above.

Furthermore, in the French VC worker cohort, we have been able to identify the effect of the XPD polymorphisms on the occurrence of both mutant biomarkers, although the most marked and statistically significant effect was on the mutant *ras*-p21 biomarker, as expected [75]. In this case, individuals who were homozygous variant at either residue 312 or 751 had a statistically significant 2.6-3.0-fold increased risk of occurrence of the mutant *ras*–p21 biomarker compared to homozygous wild-type individuals, even after controlling for potential confounders including cumulative VC exposure. Furthermore, in the case of the residue 751 polymorphism, the gene-environment interaction between the polymorphism and VC exposure, as well as the gene-gene interaction between the XPD and CYP2E1 polymorphisms (which could increase VC metabolism to its promutagenic reactive metabolites and thus also increase etheno-DNA adducts at any given level of VC exposure with a resultant increase in the mutant biomarkers) appeared to be potentially multiplicative [75]. Once again, studies in other VC worker populations have found similar effects of the XPD polymorphisms on other biomarkers of DNA damage [77].

This is also consistent with various experimental results in this model system. For example, molecular modeling of the normal and polymorphic forms of XPD demonstrates that these substitutions produce discrete local conformational changes in the protein which affect its overall structure and could affect its function [82, 84], and, in particular, are projected to interfere with its protein-protein interactions and binding to other components of the TFIIH complex (Figure 2; adapted from Gibbons et al. [85]). Also, studies of lymphoblasts from individuals of different genotypes exposed *in vitro* to the reactive metabolites of VC showed that cells with the XPD 751 homozygous variant Gln-Gln genotype had an approximate 5-fold decrease in efficiency of repair of εG DNA adducts compared to cells with the homozygous wild-type Lys-Lys genotype [82], resulting in an approximate 4.8-fold increase in mutation frequency in the polymorphic cells compared to the wild-type cells as determined by the HPRT assay, even though there is no difference in the level of expression of the XPD protein among cells that are homozygous wild-type, heterozygous or homozygous polymorphic at this codon (Figure 3). Once again, based on mutational spectrum studies in CAA-exposed human cell lines [83], the resultant increase in ▪ G DNA adducts would especially result in an increase in G->A transitions consistent with those found in the tumors of VC-exposed workers.

A thorough understanding of the molecular biology and molecular epidemiology of VC carcinogenesis can provide the basis for new molecular approaches to the prevention of VC-

induced cancers and potentially other cancers related to DNA-damaging agents. For example, one approach to secondary prevention could be based on "personalized prevention" derived from knowledge of the status of individual's DNA repair capability. Although little is currently known about methods for altering DNA repair activity, there is some evidence to suggest augmenting DNA repair may be possible. Several *in vitro* studies have shown that DNA repair processes can be increased by selenium-based compounds in response to radiation or chemically induced DNA damage [86]. More recently, a study in mice has suggested that selenocystine administration, although it did not protect against immediate DNA damage following ionizing radiation exposure, was nevertheless protective because it enhanced the rate of repair of the induced DNA damage [87]. In cohorts exposed to DNA damaging agents, determination of the dose of selenium compounds to provide an optimum effect on DNA repair could be based on the genetic status of the exposed individuals in terms of the presence of polymorphisms in key components of the repair apparatus, and the success of such interventions could be effectively monitored by following mutant biomarkers of DNA damage.

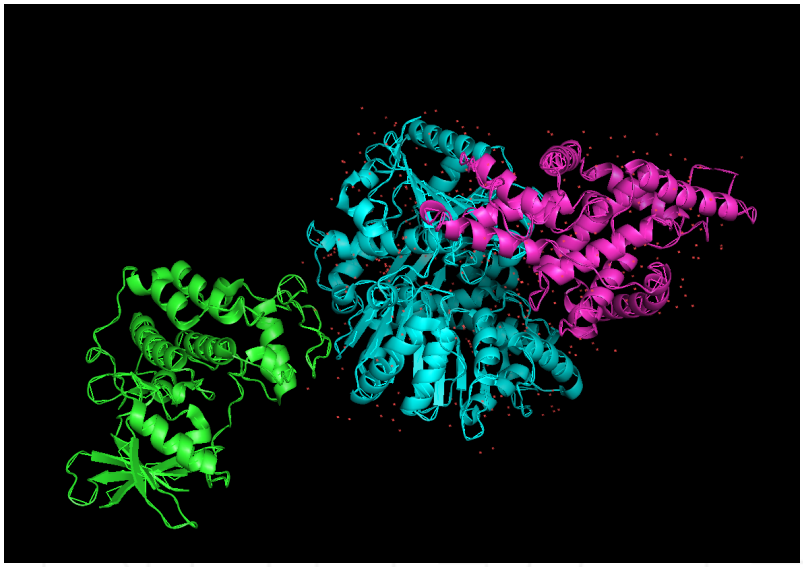

Figure 2. Protein backbone structures showing the proposed interaction effect of XPD (blue), cyclin H (pink) and cdk7 (green) in the TFIIH complex.

3. Conclusion

VC provides an instructive model for the study of the role of DNA repair polymorphisms in chemical carcinogenesis. A detailed understanding of the molecular biology of VC carcinogenesis has provided new ways of studying the molecular epidemiology of

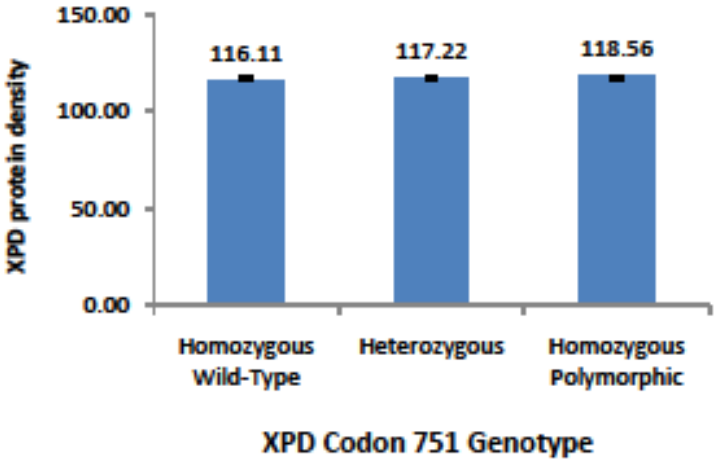

Figure 3. Levels of expression of the XPD protein in lymphocyte cell lines that are homozygous wild-type, heterozygous or homozygous polymorphic at codon 751.

VC carcinogenesis in exposed humans, which in turn may provide the basis for new approaches to the prevention and treatment of VC-related cancer. This model could also have much broader implications, since other potential carcinogenic exposures share some of the same molecular biologic pathways of damage and repair as VC similar molecular epidemiologic biomarkers could be useful for monitoring their carcinogenic process and the effect of altered susceptibility due to changes in DNA repair capability. Such studies in additional model systems would further help to define the exact significance of DNA repair polymorphisms in the development of human cancers.

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