The DNA in all cells of the human body is subject to damage continuously from endogenous processes and spontaneous decomposition. Failure to repair such damage is fundamental to the development of many diseases and to ageing. Fortunately, the vast majority of DNA damage is detected and repaired by one of five complementary DNA repair systems. However, recent studies have shown that even in healthy individuals there is a wide inter-individual variation in DNA repair capacity. Part of this variation can be accounted for by polymorphisms in the genes encoding DNA repair proteins. However, it is probable that environmental factors, including dietary exposure as well as diet–gene interactions, are also responsible for much of the difference in repair capacity between individuals. Whilst there is some evidence from human studies that generalised malnutrition or low intakes of specific nutrients may affect DNA repair, as yet there is limited understanding of the molecular mechanisms through which nutrients can modulate this key cellular process.
Table 1. Summary of human DNA repair mechanisms

<table>
<thead>
<tr>
<th>Repair pathway</th>
<th>Damage repaired</th>
<th>Sources of damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mismatch repair</td>
<td>Mismatched base pairs, small insertion loops</td>
<td>Replication errors, minor base modifications (oxidation, alkylation)</td>
</tr>
<tr>
<td>Base excision repair</td>
<td>Oxidised bases alkylation, abasic/AP sites, single-strand breaks</td>
<td>Reactive oxygen species, alkylation agents, spontaneous hydrolysis</td>
</tr>
<tr>
<td>Nucleotide excision repair</td>
<td>Bulky helix-distorting lesions</td>
<td>UV light, cigarette smoke, dietary factors (aflatoxin, PhiP, polyaromatic hydrocarbons(benzof[e]pyrine))</td>
</tr>
<tr>
<td>Double-strand break repair</td>
<td>Double-strand breaks, DNA cross-links</td>
<td>Ionising radiation, cross-linking agents (cisplatin), replication errors</td>
</tr>
<tr>
<td>Direct reversal</td>
<td>Alkylated bases: O6-methyl-guanine</td>
<td>Alkylation agents, nitrosoureas, streptozotocin</td>
</tr>
</tbody>
</table>

PhiP, 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine; AP, apurinic/apyrimidinic.

(e.g. T/C or A/G), caused by errors in DNA replication as well as alkyl adducts, and oxidatively-damaged bases are repaired by mismatch repair. One such mismatch lesion that is commonly found arises from the deamination of cytosines to uracil or methylated cytosines to thymine, which if unrepaird cause a C→T transversion post DNA replication. Mismatch repair also serves to repair small insertions and deletions in the DNA caused when the DNA polymerase ‘slips’, usually in repetitive microsatellite DNA sequences.

The process of mismatch repair involves twenty-six genes and proteins and their encoded proteins that act in three stages to remove and repair damage. First, the mismatched base is recognised by the MSH2/MSH6 heterodimer. The damaged strand around the lesion is unwound and removed, involving the MLH1/PMS2 heterodimer and other proteins. This stage leaves a single-stranded gap, which is repaired by specific polymerases and DNA ligase 1 (Jiricny & Nyström-Lahti, 2000).

**Double-strand break repair**

Double-strand breaks are the most cytotoxic and potentially mutagenic lesions that can afflict DNA, as they can quickly lead to chromosomal breaks or exchanges and cell death. Double-strand breaks are induced by ionising radiation, mechanical stress and calastogens (agents causing visible chromosomal damage) such as the chemothapeutic agent cisplatin (Pfeiffer et al. 2000). Repair of double-strand breaks may proceed through two distinct pathways: the error-free homologous recombination; the error-prone non-homologous end joining, which is crude in that it simply ligates the two ends of a double-strand break (Christmann et al. 2003). Homologous recombination uses the homology of the sister chromatid to facilitate high-fidelity repair of double-strand breaks. Homologous recombination begins with the digestion of one strand of DNA at the break site, resulting in a single-stranded 3’ overhang (Christmann et al. 2003). The RAD52 and RAD51 proteins promote the formation of nucleofilaments and facilitate interactions between the damaged strand and the undamaged DNA on the sister chromosome. Thereafter, strand exchange takes place, allowing the synthesis of new DNA across the break using the undamaged chromosome as a template.

**Base excision repair**

BER is responsible for the repair of numerous small mutagenic lesions that do not disrupt the DNA double helix. The most-frequently-repaired lesions are apurinic/apyrimidinic sites, in which the base is missing from the DNA backbone (Seeberg et al. 1995). Base deamination, oxidation and alkylation, which can cause mispairing and lead to mutations post replication are also repaired through the BER pathway. BER can be divided into three stages: damage is recognised; damaged bases are removed creating an apurinic/apyrimidinic site; apurinic/apyrimidinic sites are filled with the synthesis of new DNA. In human subjects there are eleven glycosylases that are able to recognise damaged bases and cleave them from the sugar phosphate backbone, creating an apurinic/apyrimidinic site (Hung et al. 2005). For repair to continue apurinic/apyrimidinic sites must be incised to create a single-strand break, either by the glycosylase itself or by the apurinic/apyrimidinic endonuclease enzyme. Such sites (created spontaneously, by glycosylases or by apurinic/apyrimidinic endonuclease) are repaired in one of two ways: (1) short-patch repair, in which a single nucleotide in inserted into the apurinic/apyrimidinic site by DNA polymerase β and DNA ligase; (2) long-patch repair, in which an additional two to thirteen nucleotides are removed and the gap repaired by polymerases and ligase (Christmann et al. 2003).

**Nucleotide excision repair**

NER is a complex DNA repair pathway involving over thirty genes and proteins (Friedberg, 2001) and is responsible for the repair of any DNA lesion that causes distortion to the DNA double helix. NER commonly repairs lesions induced by UV as well as numerous exogenous agents such as those derived from food and smoking, including 2-amino-1-methyl-6-phenylimidazo [4,5-β] pyridine and benz[a]pyrene diol-epoxide.

NER can be divided into two distinct pathways: global genomic repair; transcription-coupled repair. Transcription-coupled repair repairs lesions that block the progression of RNA polymerase along actively-transcribed genes. Global genomic repair is independent of transcription and acts to repair lesions in non-transcribed regions of the genome as well as those in the non-transcribed strand of DNA.
active genes. These two pathways differ only in the way DNA damage is detected, with the subsequent repair steps being identical (see Fig. 1).

In transcription-coupled repair a helix-distorting lesion located in an actively-transcribed gene halts the progression of the RNA polymerase at the site of damage. The stalling of the polymerase initiates the removal and repair of the damage, allowing transcription to continue. In global genomic repair the xeroderma pigmentosum (XP) complementation group C (XPC) protein, in association with UV excision repair protein RAD23 homologue B, recognises and binds to the helix distortion caused by the damage rather than to the lesion itself. The initiation of transcription-coupled repair is faster than the initiation of global genomic repair, presumably because of the implications of DNA damage during mRNA synthesis (Benhamou & Sarasin, 2000).

Once the site of damage has been recognised, DNA is unwound around the lesion by two helicase enzymes XPB (unwinding 3' to 5') and XPD (unwinding 5' to 3'). Both pathways converge at the site of damage.

**Fig. 1.** Overview of nucleotide excision repair pathway. XPA, XPC, XPG, xeroderma pigmentosum complementation groups A, C and G; TFIIH, transcription factor 11H; RPA, replication protein A; PCNA, proliferating cell nuclear antigen; RCF, replication factor C; POLδ, DNA polymerase δ. (Adapted from Friedberg, 2001.)
Table 2. Summary of genetic syndromes characterised by a defect in DNA repair

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of genetic disorder</th>
<th>DNA repair system disrupted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia telangiectasia</td>
<td>Autosomal recessive</td>
<td>Strand break repair</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>Autosomal recessive</td>
<td>Strand break repair</td>
</tr>
<tr>
<td>Bloom’s syndrome</td>
<td>Autosomal recessive</td>
<td>Strand break repair*</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>Autosomal recessive</td>
<td>Strand break repair</td>
</tr>
<tr>
<td>Rothman-Thomson syndrome</td>
<td>Autosomal recessive</td>
<td>Strand break repair*</td>
</tr>
<tr>
<td>Fanconi anaemia</td>
<td>Autosomal recessive</td>
<td>Strand break repair*</td>
</tr>
<tr>
<td>Hereditary non-polyposis colorectal cancer</td>
<td>Autosomal recessive</td>
<td>Mismatch repair</td>
</tr>
<tr>
<td>Xeroderma pigmentosa</td>
<td>Autosomal recessive</td>
<td>Nucleotide excision repair</td>
</tr>
<tr>
<td>Trichothiodystrophy</td>
<td>Autosomal recessive</td>
<td>Nucleotide excision repair</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>Autosomal recessive</td>
<td>Transcription-coupled nucleotide excision repair</td>
</tr>
</tbody>
</table>

*May be disruption to more than one repair pathway.

XPD and XPB are part of the basal transcription factor IIH complex, which is essential for the initiation of transcription by RNA polymerase II. This unwinding creates distinct junctions between double-stranded and single-stranded DNA, which are essential for the progression of repair (Friedberg, 2001). The damaged strand of DNA is incised at these two junctions, i.e. at the 3’ side of the damage by XPG protein and at the 5’ side by the XPF–excision repair cross-complementing rodent repair deficiency complementation group I (ERCC1) complex. This step results in cleavage and subsequent removal of approximately thirty nucleotides of single-stranded DNA containing the damage. The remaining single-stranded gap is filled by DNA polymerase δ or ε and the new strand is joined to the existing DNA by DNA ligase (de Laat et al. 1999).

Inter-individual variation in DNA repair capacity and disease

Loss, or severe impairment, of DNA repair processes results in a decrease in the ability to process DNA damage and ultimately leads to disease, most often cancer. A number of familial syndromes arise as a result of a disruption to DNA repair processes (summarised in Table 2). One such disorder is XP, which is a rare autosomal recessive syndrome characterised by a severe photosensitivity of sunlight-exposed areas of the skin from an early age. Patients with XP have inactivating mutations in any one of seven genes encoding proteins essential for NER, have ≤1000-fold increased risk of skin malignancies and are also ten to twenty times more likely to develop internal tumours at <20 years of age (de Boer & Hoeijmakers, 2000).

Fortunately, such heritable syndromes, resulting in a complete disruption to DNA repair processes, are rare and account for only a small proportion of cancer incidence. However, large inter-individual variations in DNA repair capacity have been observed in healthy populations. Qiao et al. (2002a) have found a 4-7-fold variation in NER capacity, measured using the host cell reactivation assay, in 102 healthy subjects (Qiao et al. 2002a). Also, DNA repair of UV-induced damage, measured using the unscheduled DNA synthesis assay varies over an approximately 8-fold range, again in healthy control subjects (Mohankumar et al. 1998). Amongst sixty-three young (mean age 21 years) healthy volunteers recruited to the Dietary Antioxidant Repair Trial there is a 10-fold inter-individual variation in NER capacity, measured using the host cell reactivation assay (see Fig. 2; Tyson et al. 2005).

Inter-individual variation in DNA repair capacity within the general population is believed to be associated with cancer risk. Case–control studies have shown that cancer patients have a repair capacity below that of healthy matched controls. For example, reduced NER capacity has been associated with increased risk of cancer of the skin, lung, head and neck, and breast (Ana et al. 2005). Additionally, there may be links between recombination repair and sporadic breast cancer (Ralhan et al. 2006) and a reduced BER capacity may also increase risk of lung cancer (Paz-Elizur et al. 2003). In a review of studies carried out before1998 it has been concluded that there is a consistent positive correlation between reduced DNA repair capacity and cancer occurrence, with OR of between 1.4 and 75.3 (Berwick & Vineis, 2000). However, as yet no prospective studies have been conducted and a reduced DNA repair capacity could be a result of, rather than a cause of, cancer.

The possible reasons for the substantial inter-individual variation in DNA repair capacity may include genetic factors, such as polymorphisms in DNA repair genes, and variation in environmental exposure, including dietary and lifestyle factors. For example, variation in DNA repair is partly attributable to variations in age and BMI, both of which are inversely associated with NER capacity (Tyson et al. 2006).

Genetic polymorphisms, DNA repair and cancer risk

Common genetic polymorphisms in DNA repair genes have been associated with the inter-individual variation in DNA repair and also with cancer risk. The majority of genes encoding proteins important in DNA repair are polymorphic (Mohrenweiser et al. 2002). For example, there are a number of polymorphisms in the ERCC2 gene...
that encodes for the XPD protein, a DNA helicase essential for NER. The ERCC2 Asp312Asn single-nucleotide polymorphism (SNP) has a modulatory effect on both NER capacity and adduct levels, with carriers of one or more of the Asn alleles showing reduced repair capacity (Spitz et al. 2001) and increased adduct levels (Hou et al. 2002; Tang et al. 2002) compared with homozygotes of the Asp allele. In addition, the Gln allele of the ERCC2 Lys751Gln SNP has been associated with both reduced NER capacity (Spitz et al. 2001; Qiao et al. 2002b) and increased prevalence of adducts (Palli et al. 2001; Hou et al. 2002; Tang et al. 2002). Similar effects are seen in other repair systems, with variants of the BER proteins 8-oxoguanine DNA glycosylase 1 and X-ray cross-complementing group 1 showing reduced activity (Pachkowski et al. 2006; Sokhansanj & Wilson, 2006).

The same polymorphisms that appear to modulate repair capacity have been associated with cancer risk. Again, polymorphisms of the ERCC2 gene are implicated, with carriers of the uncommon alleles being found in greater frequencies amongst groups of cancer sufferers than amongst controls (Bennhamou & Sarasin, 2005). Also, polymorphisms in BER genes are often found to convey increased cancer risk (Hung et al. 2005). A meta-analysis of BER polymorphisms and cancer risk (Hung et al. 2005) has shown that Cys/Cys homozygotes for the 8-oxoguanine DNA glycosylase 1 Ser326Cys polymorphism have an increased risk of lung cancer (OR 1.24) and the carriers of the Trp allele of the X-ray cross-complementing group 1 194Trp SNP are protected against tobacco-related cancers.

However, such genetic associations with repair capacity and with cancer risk are not observed consistently. For example, in contrast to the other findings the ERCC2 Lys751Gln SNP has been reported to have no effect on NER capacity (Qiao et al. 2002b), adduct levels (Duell et al. 2000) or cancer risk (Bennhamou & Sarasin, 2005). This lack of reproducibility in genetic-association studies is common and may arise for a number of reasons. Differential findings may be related to differences in study size and statistical power, with large studies having greater power to detect smaller effects. Alternatively, the interactions between genetic and environmental factors could be important, with the effect of genotype being apparent only in certain environmental settings. Finally, polymorphisms believed to affect repair capacity and cancer may be in linkage disequilibrium with neighbouring polymorphisms in the same or adjacent genes.

The effect of multiple polymorphisms in NER genes on NER repair capacity has been investigated. In the Dietary Antioxidant Repair Trial (Tyrson et al. 2006) NER capacity was measured in sixty-three subjects who had been genotyped for polymorphisms in key NER genes. Here, two significant gene–gene interactions were found when subjects were grouped according to genotype for each polymorphism based on the presence or absence of the uncommon allele. The XPC Lys939Gln SNP appears to interact with both the ERCC5 Asp1104His and the ERCC2 Lys751Gln SNP (P = 0.01 and P = 0.03 respectively), with repair capacity being dependent on specific allelic combinations of the polymorphisms. In the case of ERCC5 Asp1104His SNP repair capacity appears to be independent of the Asp allele, whereas carriers of the His allele show high repair in the absence of the Gln allele of the XPC Lys939Gln SNP and low repair in the presence of this SNP. In the case of the ERCC2 Lys751Gln SNP repair capacity is independent of the presence the Gln allele, but homozygotes of the Lys allele have a high repair capacity in the absence of the Gln allele of the Lys751Gln SNP and low repair capacity in the presence of this SNP.

**Nutritional modulation of DNA repair**

There is a clear link between diet and cancer, with variation in diet accounting for over one-third of the variation in cancer incidence (Doll & Peto, 1981). Epidemiological evidence shows convincingly that diets rich in fruit and vegetables are associated with a decreased risk of cancer of the lung, mouth, pharynx, oesophagus, colon and rectum (World Cancer Research Fund/American Institute for Cancer Research, 1997). There are also probable risk reductions for laryngeal, pancreatic, breast and bladder cancers associated with such diets (World Cancer Research Fund/American Institute for Cancer Research, 1997). More recently, the European Prospective Investigation into Cancer and Nutrition Study has shown that diets low in fibre (Bingham et al. 2003) and/or high in red meat are associated with an increased risk of colorectal cancer (Gonzalez et al. 2002; Norat et al. 2005). Much effort has been put into defining the dietary constituents and the biological mechanisms underlying the protective effects of diet on cancer. Many studies (see Moller & Loft, 2004) have investigated the effects of dietary components on levels of DNA damage. However, DNA damage is only of consequence if it cannot be adequately repaired, so that the individual’s ability to perform DNA repair may be at least as important as the damage they sustain.

To date a relatively small number of studies (summarised in Table 3) have investigated the influence of diet or nutrient status on DNA repair processes. Perhaps not
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>DNA repair measurement</th>
<th>Subjects</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moller &amp; Loft (2004)</td>
<td>Blinded placebo-controlled intervention. Three treatment groups: (1) slow release vitamin C + vitamin E; (2) plain release vitamin C + vitamin E; (3) placebo. Treated for 4 weeks</td>
<td>OGG1 mRNA levels</td>
<td>Forty-eight male smokers (20–65 years)</td>
<td>No effect of intervention on OGG1 expression</td>
</tr>
<tr>
<td>Moller et al. (2003)</td>
<td>Intervention study. Parallel design with subjects treated for 24 d with: (1) 600g fruit and vegetables; (2) tablets providing ‘same’ amount of antioxidants and minerals; (3) placebo</td>
<td>OGG1 and ERCC1 mRNA levels</td>
<td>Forty-three subjects (twenty-one female) aged 21–56 years</td>
<td>No effect of intervention on OGG1 or ERCC1 expression</td>
</tr>
<tr>
<td>Collins et al. (2003)</td>
<td>Randomised cross-over intervention study. Subjects supplemented with one, two and three kiwi fruit for 3 weeks with 2-week wash-out periods between treatments</td>
<td>BER capacity using a modified comet assay and OGG1 and APE1 mRNA levels</td>
<td>Fourteen (eight female) healthy non-smokers aged 26–54 years</td>
<td>Increase in BER capacity after supplementation, independent of no. of kiwi consumed. No change in OGG1 or APE1 expression</td>
</tr>
<tr>
<td>Tomasetti et al. (2001)</td>
<td>Intervention study. Subjects took 100 mg ubiquinine-10 for 1 week</td>
<td>BER capacity using a modified comet assay</td>
<td>Six healthy non-smokers (three female) aged 26–54 years</td>
<td>Significant (P&lt;0.05) 2-7-fold increase in repair capacity after supplementation</td>
</tr>
<tr>
<td>Astley et al. (2004)</td>
<td>Intervention study. Subjects assigned to treatment group and asked to take one of the following for 3 weeks: (1) 200 g cooked minced carrots; (2) total of 11·9 mg α- and β-carotene + 1·75 mg α-tocopherol; (3) 298 g tinned mandarins, 60 mg vitamin C; (4) placebo capsules</td>
<td>The repair of single-strand breaks and oxidative lesions was measured using a patch synthesis assay</td>
<td>Sixty-four healthy male subjects aged 18–50 years</td>
<td>Repair capacity increased significantly (P&lt;0.05) only after treatment 1 (supplementation with the cooked minced carrots). No effect of treatments 2, 3 or 4</td>
</tr>
<tr>
<td>Sheng et al. (1998)</td>
<td>Intervention study. Subjects supplemented with a combination of nicotinamide, Zn and carotenoids for 7 weeks</td>
<td>Followed repair of H2O2- induced DNA damage over time using the comet assay</td>
<td>Four healthy volunteers</td>
<td>Significant increase in repair seen (P&lt;0.01) post supplementation</td>
</tr>
<tr>
<td>Chiricolo et al. (1993)</td>
<td>Intervention study. Children with Down syndrome (DS) and healthy controls were given 1 mg Zn/kg body weight for 4 months</td>
<td>Repair of γ- radiation followed using alkaline elution assay</td>
<td>Fifteen children in each treatment group, mean age 9 years</td>
<td>‘Abnormally’ high repair rates in DS children pre-supplementation was returned to normal by Zn supplementation. No effect of supplementation in control group</td>
</tr>
<tr>
<td>Basten et al. (2006)</td>
<td>Blinded placebo-controlled intervention in human subjects supplemented with 1·2 mg folic acid or a placebo daily for 6 weeks</td>
<td>BER capacity using a modified comet assay</td>
<td>Sixty-one healthy subjects (20–60 years), thirty supplemented, thirty-one placebo control</td>
<td>No effect of folic acid on BER activity</td>
</tr>
<tr>
<td>Wei et al. (2003)</td>
<td>Retrospective observational study. Assessed dietary folate intake using FFQ</td>
<td>NER capacity using HCR assay</td>
<td>559 individuals with no malignancies, (mean age 61 years)</td>
<td>18% reduction (P&lt;0.01) in repair capacity in those in the lowest tertile of folate intake compared with those in the highest tertile</td>
</tr>
<tr>
<td>Gonzalez et al. (2002)</td>
<td>Observational study of Mexican children. Three groups studied: (1) well-nourished non-infected; (2) well-nourished infected; (3) malnourished infected</td>
<td>Followed repair of H2O2- induced DNA damage over time using the comet assay</td>
<td>Nineteen children aged 6–26 months</td>
<td>The malnourished infected children had a significantly (P&lt;0.05) lower repair capacity than the other two treatment groups</td>
</tr>
</tbody>
</table>

OGG1, 8-oxoguanine DNA glycosylase 1; ERCC1, excision repair cross-complementing rodent repair deficiency complementation group 1; BER, base excision repair; APE1, human apurinic endonuclease 1; NER, nucleotide excision repair; HCR, host cell reactivation.
Mechanisms through which diet may modulate DNA repair processes

As there has been limited research into the dietary modulation of DNA repair, there is little direct evidence for biological mechanisms through which DNA repair processes may be modified by diet. However, a number of possible mechanisms can be, and have been, proposed based on previous observations and knowledge of how diet can affect other cellular processes. Diet may modify DNA repair through changes at the level of transcription, although effects on mRNA stability translation, protein stability and protein trafficking should also be considered. Candidate mechanisms through which nutrients and other dietary components may influence gene expression have been reviewed recently (Mathers, 2006). The availability of any nutrient necessary for the proficient synthesis of DNA, RNA and proteins may impact on DNA repair processes. This factor may explain the decreased BER capacity of malnourished children reported by Gonzalez et al. (2002), although as yet there is no direct mechanistic evidence.

Some of the most convincing indirect mechanistic evidence in this area comes from in vitro work with Se, which (in the form of selenomethionine) increases NER capacity 2-fold in human fibroblast cells (Seo et al. 2002b). Follow-up work (Seo et al. 2002a) has found that this Se-induced increase in repair is dependent on both P53 and the protein redox factor-1, with Se reducing specific cytosine residues on P53. Furthermore, this Se-dependent reduction of P53 is lost in cells lacking redox factor-1, suggesting that redox factor-1 is an intermediary in the Se-dependent activation of P53. It has now been demonstrated (Fischer et al. 2006) that Se-induced activation of P53 is also dependent on the presence of the BRCA1 protein, which is believed to be important in recombination repair and is frequently mutated in heritable breast cancer.

A further mechanism through which Se may influence DNA repair is through alterations to the binding activity of transcription factors and DNA repair proteins. Using mobility shift assays in an extracellular system it has been
shown (Handel et al. 1995) that Na$_2$SeO$_3$ (1 μM) inhibits binding of the transcription factor activator protein-1 to its consensus DNA sequence by 50%. Similar effects on consensus sequence binding of NF-κB, as well as transcription factors SP-1 and SP-3, have been reported (Youn et al. 2001). More specifically, reducible Se compounds inhibit the NER protein XPA and the BER protein formamidopyrimidine DNA glycosylase, both of which belong to a family of DNA-binding proteins (Blessing et al. 2004), known as Zn finger proteins, in which Zn atoms are complexed with cysteine and/or histidine residues, forming domains through which the protein can bind DNA. Reducible Se compounds lower the removal of oxidative damage by the formamidopyrimidine DNA glycosylase enzyme and binding of the XPA protein in a dose-dependent manner (Blessing et al. 2004). Zn atoms are released from both XPA and formamidopyrimidine DNA glycosylase on Se treatment, suggesting that the displacement of Zn from Zn fingers results in inactivation of the protein. Approximately 3% of all proteins contain Zn finger motifs, including P53 and several other important DNA repair proteins. Thus, disruption to their functional domains could exert wide-ranging effects on DNA repair and other cellular processes. The intake and bioavailability of Zn itself may be of importance, since adequate Zn status is required for optimal functioning of these proteins (Ho, 2004).

An additional important mechanism through which diet may influence DNA repair is via hypermethylation of CpG islands (short stretches of DNA with a higher frequency of the CG sequence) in the promoter regions of repair genes, leading to gene silencing. The O$^6$-methylguanine-DNA methyltransferase (which repairs alkylated guanine bases; Nakagawachi et al. 2003) and MLH1 (a key component of mismatch repair; Feinberg & Tycko, 2004) genes are both silenced by promoter hypermethylation during tumorigenesis. Folate may alter DNA methylation via its role as a methyl donor and thus influence the expression of key DNA repair genes. Other dietary factors, including Zn, Se and vitamin C, may also alter DNA methylation (Friso & Choi, 2002).

Given its apparent benefit in extending longevity in rodents and some other animals, it is interesting to note the effects of energy restriction on DNA repair capacity, which to date has been investigated in four animal studies (Guo et al. 1998; Cabellof et al. 2003; Stuart et al. 2004; Gedik et al. 2005). Rats fed an energy-restriction diet do not show the age-related decline in either BER (Cabellof et al. 2003) or NER (Guo et al. 1998) seen in rats fed an unrestricted diet. A third study (Gedik et al. 2005) has found that energy restriction has no effect on the repair of peroxide-induced strand breaks in ageing rats. However, in the latter study the aged rats were sampled at 17 months as compared with 24 months in the first two studies. Furthermore, DNA repair was quantified by inducing strand breaks, not by following the repair of DNA adducts as in the previous two studies. A fourth study (Stuart et al. 2004) has found that the activity of specific BER enzymes in liver, but not kidney, tissue increases in mice fed an energy-restriction diet. Here, the effects of ageing were not considered, and it is yet to be established whether energy restriction can enhance DNA repair or simply prevent its age-related decline. The results of the Stuart et al. (2004) study also suggest that tissue-specific differences in repair should be considered in future observational and intervention studies.

One of the most obvious ways in which energy restriction could affect DNA repair is through altered gene expression. Animal studies have shown that energy restriction alters the expression of numerous genes, including those involved in DNA repair pathways (Lee et al. 1999; Weindruch et al. 2001). Energy restriction is known to reduce the production of harmful oxygen species, and it may also alter protein synthesis and immune function (Dirx et al. 2003). It is possible that one or more of these effects may contribute to the changes in DNA repair associated with reduced energy intake. Increased DNA repair capacity could contribute to the increased lifespan and reduced age-associated changes seen in organisms in which energy intake is restricted.

**Concluding remarks**

DNA damage if unrepaired leads to aberrant gene expression, which is fundamental to the initiation and progression of many diseases. Much research aimed at understanding the beneficial health effects of diet and dietary components has focused on DNA damage. However, DNA damage is only of consequence if left unrepaired. It is clear that interindividual variation in DNA repair capacity in apparently healthy populations is high and that there may be important implications for disease risk if the capacity for DNA repair is suboptimal. This inter-individual variation in DNA repair capacity is explained in part by polymorphisms in the genes that encode DNA repair proteins. However, to date it has not been shown that any single polymorphism can account consistently for variations in DNA repair capacity, and future studies should utilise high-throughput genomic technologies to assess the effects of multiple polymorphisms on repair capacity.

Although only a limited number of studies have investigated the effects of diet and dietary factors on DNA repair processes, the results support the hypothesis that nutrition may have an important influence on DNA repair. There is some evidence that whole diet and specific dietary components and nutrients can modify DNA repair processes. However, further investigations will be required to determine which components of the diet affect DNA repair and to establish intake levels that optimise repair capacity.

As with several other areas of human physiology, interactions between environmental exposure, especially dietary exposure, and genetic make up will be an important area of investigation. Future studies should address the hypothesis that dietary exposure may have different effects on health depending on the genetic background of the individual. Progress in this area will be helped by the development of high-throughput technologies for quantifying DNA repair capacity and by more objective and less-labour-intensive methods for assessing dietary exposure.
Acknowledgments

We acknowledge collaboration by the Dietary Antioxidant Repair Trial team, including John Hesketh, Fiona Caple, Alison Spiers, Ann Daly and Elizabeth Williams, and funding from the BBSRC (project no. 13/D15721). J.T. is funded by a BBSRC studentship (02/B1/D/08297).

References


