Chapter 2
Susceptibility to MDS: DNA Repair and Detoxification Genes

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Introduction

The myelodysplastic syndromes (MDS) are a collection of heterogeneous disorders arising from a clonal myeloid stem cell. They are characterised by ineffective haematopoiesis and are frequently associated with genetic instability manifested as chromosomal abnormalities. MDS progresses through a pathway of one or more dysplasias and ends in myeloid leukaemia—the risk of developing acute myeloid leukaemia (AML) depends on the subtype of MDS. Similar to other malignant diseases, the stepwise disease progression is likely to be the consequence of the accumulation of mutations, probably due to an increased DNA damage burden and/or reduced ability to deal with the damage.

MDS risk has previously been associated with benzene exposure or exposure to a number of other environmental toxins. In addition a subset of patients develop the disease following chemotherapy or radiotherapy treatment for a primary disease (therapy-related MDS (t-MDS)). Mammalian cells have a number of efficient systems designed to metabolise and inactivate harmful genotoxic agents, or if the agents manage to induce damage then complex DNA repair mechanisms effectively remove the damage. Importantly, if the damage is excessive, DNA damage response proteins will trigger the apoptotic pathway to get rid of the cell for the good of the whole organism. These systems are not only required for protection from exogenous damaging agents but also for the constant damage cells receive from endogenous cellular processes, predominantly oxidative stress.

MDS incidence increases with increasing age suggesting that the genotoxic burden on DNA eventually reaches a critical level resulting in disease. What, however, predisposes some individuals to the development of MDS when they have encountered a similar level of damage as an individual who remains healthy? A large body

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of research suggests that the answer, at least in part, is genetic variation in key genes involved in (1) protection of cellular entities from damage and (2) repair of DNA damage. Mutations in these genes are rare but of high penetrance and lead to serious genetic diseases; one example of a disease arising from mutations in DNA repair genes is Fanconi Anaemia which carries a strong predisposition to MDS. Much more common are genetic polymorphisms that occur in many of the genes which function to protect our genomes. This chapter aims to summarise research published on polymorphisms in detoxification and DNA repair genes in MDS. Therapy-related MDS is rarely investigated alone but is commonly grouped with therapy-related AML and indeed t-AML and t-MDS are now classified together by the World Health Organisation. There is a great deal of research that has been done on polymorphisms in t-AML/MDS (reviewed in Seedhouse and Russell [67]), so we will concentrate on work performed on de novo MDS samples and only positive associations of polymorphisms with t-AML/MDS will be discussed.

Detoxification Pathways

The first line of defence to genotoxic agents is detoxification—this should occur before the agents are able to damage cellular molecules. Metabolism of endogenous and exogenous agents occurs by the same pathways and is divided into two phases. Phase I involves activation of substrates into electrophilic intermediates; these reactions are predominantly catalysed by the cytochrome P450 (CYP) protein family, many of which harbour polymorphisms which affect their function. The products of the phase I reactions are highly reactive and liable to cause severe cellular damage and the phase II enzymes (conjugation) are required to inactivate the phase I products. Enzymes that participate in phase II include the glutathione S-transferases (GST) and NAD(P)H:quinine oxidoreductase-1 (NQO1). These enzymes not only detoxify reactive phase I products but also act on genotoxic agents that do not require phase I activation.

The balance of phase I and II activity is critical and a consequence of high levels of phase I activity with low levels of phase II activity is the production of deleterious metabolites which will damage cell components, especially DNA. It follows that polymorphisms affecting the function of either phase I or II proteins, or indeed proteins from both phases, may upset the balance of detoxification activity and predispose individuals to high levels of damaging agents.

Phase I: Cytochrome P450 Enzymes

The cytochrome P450 superfamily comprises a large and diverse group of membrane-associated haem-proteins divided into 18 families. They are responsible for the metabolism of both endogenous and exogenous substrates, largely via an oxidative reaction, creating highly reactive intermediates that cause damage to DNA

unless detoxified by phase II proteins (reviewed in Nebert and Dalton [53]). The CYP proteins can be induced or inhibited resulting in highly variable expression. In addition polymorphisms exist in many of the family members which affect the function of the protein and contribute to high inter-individual variability. The allele frequencies of several of the polymorphic variants have been examined as potential disease risk-factors in MDS populations.

CYP2E1

CYP2E1 harbours a C to T single nucleotide polymorphism (SNP) in its 5′ promoter (CYP2E1*5) which is associated with increased transcriptional activity [30]. CYP2E1 is known to play an important role in the metabolism of benzene, exposure to which is a known risk factor to MDS. The CYP2E1*5B polymorphism has been studied to establish whether the variant allele increases susceptibility to benzene poisoning and hence MDS but no association was found [64].

CYP3A4

An A to G SNP is present in the CYP3A4 5′ promoter (CYP3A4*1B). The variant was initially proposed to alter a regulatory element within the promoter with a resulting decrease in activity [63]. Conversely, further biological assays failed to demonstrate specific functional differences between the variant and wild-type alleles [76, 85]. Fabiani et al. found no risk for MDS associated with CYP3A4*1B [23].

CYP3A5

Two SNPs exist within CYP3A5 (CYP3A5*3 and CYP3A5*6) both of which cause alternative splicing and truncated proteins resulting in the absence of CYP3A5 [40]. The frequencies of these polymorphisms have been studied in a Taiwanese MDS population. There was no difference in the distribution of the CYP3A5*3 allele in MDS when compared to a healthy control cohort and the CYP3A5*6 allele was not found in cases or controls [46].

Significant Findings of CYP Variants in t-AML/MDS

A large number of studies have been published examining the distribution of several of the CYP variant alleles in t-AML/MDS (reviewed in Seedhouse and Russell [67]). However, the only significant findings have been concerning the CYP3A4 A to G 5′ promoter polymorphism. The polymorphic variant (CYP3A4*1B) was found to be under-represented in a group of 30 childhood t-MDS/leukaemia samples when compared to a control group of paediatric patients with de novo leukaemia (odds ratio (OR) 0.09; 95% confidence intervals (CI) 0.01–0.87) [24] suggesting that the

variant allele may result in a decrease in DNA-damaging reactive intermediates and therefore protect against t-AML/MDS. These results were corroborated by Rund et al. [65] when comparing healthy controls with adult t-AML/MDS patients.

Phase II: Glutathione S-transferases

The glutathione S-transferase (GST) multigene family is a major class of phase II detoxification enzymes. Their substrates are manifold and include environmental mutagens, drugs and products of oxidative stress which may, or may not, be by-products of a phase I reaction. The mode of action of the GSTs is conjugation of the reactive electrophilic substrates to glutathione. There are at least four cytosolic GST subfamilies: alpha (A), mu (M), pi (P) and theta (T) and functionally relevant polymorphisms exist in each subfamily.

GSTM1 and GSTT1

GSTM1 and GSTT1 have attracted considerable interest because both genes are commonly deleted [61, 70]. The homozygous deletion GSTM1 polymorphism exists in approximately 50% of Caucasians and the GSTT1 deletion in 25%; these frequencies differ between races. Most studies examining the cellular consequences of the GSTM1 or GSTT1 deletions point towards reduced detoxification activity resulting in higher levels of DNA damage [15, 32, 73, 86, 87]. A large number of studies have examined the importance of the GSTM1 and GSTT1 deletions in MDS (summarised in Table 2.1) with some finding positive associations for either GSTM1 null, or GSTT1 null, or for the combined GSTM1 and GSTT1 null genotypes with MDS.

Dahabreh et al. have performed a meta-analysis of GSTM1 and GSTT1 deletion polymorphisms in MDS [20]. They identified 13 eligible studies for GSTT1 comprising a total of 1,471 cases and 1,907 controls. Using both fixed and random effects models the GSTT1 null genotype was shown to be significantly associated with an increased risk of MDS (Fixed effects OR 1.44, 95% CI 1.21–1.72, $p<0.0001$; random effects OR 1.43, 95% CI 1.09–1.89, $p=0.01$). This study provides strong evidence that the GSTT1 null genotype is associated with MDS susceptibility. For GSTM1, ten eligible studies were identified totalling 1,161 cases and 1,668 controls. Neither the fixed or random effects models showed an association between GSTM1 null and MDS.

When MDS patients are divided into further sub-groups the majority of studies have shown a trend for the GSTT1 null genotype being more prevalent in the RA/RARS FAB subtypes than the more aggressive RAEB/RAEB-T subtypes; however no study has reached statistical significance. Within the subgroup analyses one paper of particular interest is by Stavropoulou et al. [77] who studied a large series of well characterised MDS patients ($n=323$) enabling analysis of genotype

Table 2.1 Summary of de novo MDS studies on GSTM1 and GSTT1 polymorphisms

	Control population	MDS deletion frequency (%)	Control deletion frequency (%)	OR (95% CI)	Reference
GSTM1 deletion					
92 MDS	201 cancer-free, similar age, sex and race	42	48	0.8 (0.5–1.3)	[16]
166 MDS	112 haematologically normal staff and patients	55	48	0.89 (0.5–1.43)	[7]
116 MDS	43 healthy volunteers	55	53	0.80 (0.62–2.43)	[66]
54 MDS	60 cancer-free, matched for age and sex	57.4	33.3	2.70, $p < 0.01$	[80]
49 MDS	102 newborn	36.7	36.9	0.9. (0.5–1.9)	[6]
128 MDS	239 healthy, similar sex and race	53	51	Not given, non-significant	[27]
73 MDS[a]	Garte et al.[b] [26]	70	52	2.32, $p = 0.002$	[78]
302 MDS	330 healthy, matched for age and sex	35.4	42.4	$p = 0.086$	[77]
86 MDS	99 hospitalised controls, matched for age and sex	47.7	48.5	Not given, non-significant	[81]
157 MDS	155 cancer-free, matched for age and sex	51.6	59.4	0.73 (0.45–1.17), $p = 0.2$	[23]
GSTT1 deletion					
92 MDS	190 cancer-free, similar age, sex and race	46	16	4.3 (2.5–7.4)	[16]
166 MDS	112 haematologically normal staff and patients	21	16	0.72 (0.4–1.34)	[7]
57 MDS	100 haematologically normal staff and patients	28	23	Not given, non-significant	[9]
59 MDS	50 normal controls	46	46	Not given, non significant	[59]
158 MDS	100 blood donors, similar age and sex	21	19	Not given, non-significant	[62]
116 MDS	43 healthy volunteers	53	30	2.65 (1.27–5.52) $p < 0.01$	[66]
54 MDS	60 cancer-free, matched for age and sex	11.1	6.66	1.75, not significant	[80]
49 MDS	102 newborn	14.2	18.1	0.7 (0.2–1.8)	[6]
128 MDS	239 healthy, similar sex and race	22	16	Not given, non-significant	[27]
73 MDS[a]	Garte et al.[b] [26]	36	15	1.81, $p < 0.001$	[78]
323 MDS	330 healthy, matched for age and sex	17.9	15.8	$p = 0.518$	[77]
86 MDS	99 hospitalised controls, matched for age and sex	19.8	25.3	Not given, non-significant	[81]
156 MDS	155 cancer-free, matched for age and sex	24.4	18.1	1.46 (0.82–2.62), $p = 0.22$	[23]
Combined GSTM1 and GSTT1 deletions					
49 MDS	102 newborn	6.1	10.8	1.2 (0.2–4.7)	[6]
128 MDS	239 healthy, similar sex and race	7.8	8.8	Not given, non-significant	[27]
86 MDS	99 hospitalised controls, matched for age and sex	5.8	13.1	Not given, non-significant	[81]
73 MDS[a]	Garte et al.[b] [26]	26	7	2.86, $p < 0.001$	[78]
116 MDS	43 healthy volunteers	33	21	1.84 (0.81–4.19)	[66]
54 MDS	60 cancer-free, matched for age and sex	3	0	–	[80]
294 MDS	330 healthy, matched for age and sex	6.8	6.1	$P = 0.830$	[77]

Studies showing significant associations with MDS are shaded

[a]Only Caucasian results shown, other racial groups had very low numbers ($n \leq 10$)

[b]Published gene frequencies of healthy human subjects sorted by race ($n > 15000$)

frequencies within specific cytogenetic groups. They discovered that none of the five patient samples with an isolated 5q deletion were GSTT1-null and also noted that, in a previous publication, there were 0/10 del5q patients who had a GSTT1 null genotype [62]. By increasing their data set to 47 samples (22 of which had an isolated 5q-, 4 a 5q- with one additional abnormality and 21 a -5/del5q as part of a complex karyotype) Stavropoulou et al. found only two samples with a GSTT1 null genotype. This was highly significant when comparing to MDS samples with other karyotypic abnormalities or to the normal controls. These striking findings were explained by the fact that exposure to organic solvents had previously been associated with chromosome 5q abnormalities and that GSTT1 enzyme activity is required for some organic solvents to form mutagenic metabolites. Hence Stavropoulou et al. hypothesised that the presence of the GSTT1 gene is not always protective but may confer MDS risk following particular chemical exposure by promoting specific genetic damage.

GSTP1 and GSTPA1

The third polymorphic GST which has been widely studied in disease-risk is GSTP1. This gene has a G to A SNP which results in an ile to val amino acid change at codon 105 of the protein [1]. Codon 105 resides in the electrophile-binding site of the GSTP1 protein and the altered properties of the val amino acid affects both the catalytic activity of the enzyme, in a substrate-dependent manner, and its thermal stability.

Two studies have been published examining the contribution of the GSTP1-105 polymorphism to de novo MDS risk, the first found no positive association [66], whilst Fabiani et al. in the latter study found an increased risk of MDS associated with the presence of at least one variant val allele (OR1.66, 95% CI 1.03–2.67; $p=0.04$) [23]. Furthermore patients with low/intermediate risk MDS (IPSS risk group low/intermediate-1) had a higher probability of overall survival if they harboured a GSTP1-105 val allele ($p=0.008$). Fabiani and colleagues also examined the GSTPA1-C69T promoter variant in their study. This polymorphism has been shown to be correlated with GSTA1 expression [19]. There was no association between the GSTP1A-69T variant and MDS risk.

Significant Findings of GST Polymorphisms in t-AML/AML

A comprehensive summary of GST polymorphisms in t-AML/MDS can be found in Seedhouse and Russell [67]. Two studies demonstrated significant associations between the GSTT1 null polymorphism and t-AML/MDS disease incidence [2, 66]. In addition Allan et al. showed that individuals with at least one GSTP-105Val allele were significantly over-represented in t-AML/MDS when compared with either a control or a de novo AML group. The odds ratio was increased if only those patients

who had received chemotherapy were considered and further increased in the subgroup of patients who had prior exposure to a known GSTP1 substrate. Subgroup analysis by Haase et al. [27] also provided interesting results with a highly significant increase in the risk of developing t-MDS/AML following breast cancer treatment when the double GSTM1/GSTT1 null genotype was present. This was further pronounced when considering patients who had been treated with chemotherapy for their breast cancer.

NAD(P)H: Quinone Oxidoreductase (NQO1)

NQO1 uses NADH or NADPH to catalyse 2- or 4-electron reductions of its quinone substrates thereby producing less reactive hydroquinones. This activity plays a critical role in detoxification preventing the generation of ROS and free-radicals that would otherwise go on to damage DNA and other cellular components. The NQO1 gene has a well studied C to T SNP at position 609 resulting in a pro to ser amino acid substitution at codon 187 [79]. The variant ser-containing protein has negligible enzymatic activity and is no longer inducible in bone marrow cells following benzene metabolite exposure. An allele dosage effect occurs with the ser/ser homozygote having no activity and the pro/ser heterozygote showing intermediate activity between the homozygote variant and wild type proteins [51, 74]. Benzene poisoning is associated with a very strong risk of MDS development and the NQO1 serine allele increases the risk of benzene poisoning [64], there has therefore been interest in the distribution of the NQO1 polymorphism in MDS. Whilst no relationship has been found between the NQO1 SNP and de novo MDS risk [23, 43], these results are contrary to findings from several studies on the therapy-related disease (see below).

Significant Findings of NQO1-Pro187Ser in t-AML/MDS

Larson et al. found a significant over-representation of the NQO1-187ser allele in a t-AML/MDS cohort: interestingly 7/8 of the ser/ser homozygotes had abnormalities of either chromosome 5 and/or 7 [43]. Naoe et al. [52] confirmed these findings in 58 t-AML/MDS patients with the ser variant homozygous genotype conferring an odds ratio of 2.62 (95% CI 2.16–3.08) although chromosome 5 and/or 7 abnormalities were not over-represented in their variant homozygote samples.

DNA Repair

Cells encounter constant attack from molecules which can damage DNA. Efficient detoxification mechanisms limit cellular damage but, even so, DNA cannot be entirely spared and therefore complex pathways are present to repair DNA damage

and minimise its deleterious effects. The balance of DNA repair is critical—whilst too little repair can result in the acquisition and persistence of mutations and genetic instability, too much repair can be equally harmful by inhibiting the apoptotic pathway and enabling a cell with badly damaged DNA to attempt repair, possibly misrepair and survive. DNA damage is known to accumulate with age and eventually overloads the repair systems leading to haeamatopoietic stem cell (HSC) exhaustion. A number of studies using mouse models have effectively demonstrated the importance of DNA repair genes, involved in a number of different repair pathways, in maintaining HSC function (reviewed in Niedernhofer [55]).

MDS is primarily a disease of the elderly and some cases can occur following large genotoxic insults such as chemotherapy drug treatment. If the damage levels sustained with increasing age or genotoxic insult are unrepaired and reach a certain threshold, protective cell senescence or apoptosis should be triggered. If these mechanisms fail then the genomic instability may prime stem cells for further mutation development and functional cellular abnormalities ultimately resulting in MDS and/or leukaemia.

There is a significant body of research demonstrating high levels of DNA damage in MDS samples. Increased levels of the major oxidative damage product, 7,8-dihydro-8-oxoguanine (8-oxoG), have been found in MDS patient bone marrow samples when compared to normal bone marrow controls [33] and increased levels of oxidised pyrimidine nucleotides are seen in CD34+ enriched MDS bone marrow samples compared to either CD34− MDS samples or CD34+ bone marrow cells from normal subjects [60]. Novotna et al. have also shown higher levels of oxidative damage and genetic instability in samples from MDS patients when compared to age matched controls [56, 57]. It is not clear whether the increased DNA damage is a cause, or a result, of the MDS disease. Whilst genetic instability is one of the main prerequisites for disease development, once the disease is established iron overload in transfusion-dependent patients and reactive oxygen species generation from inflammation also have to be considered among important factors in determining the burden of DNA damage. Whatever the case, the additional DNA damage burden means that aberrant activities of DNA repair genes are likely to be particularly important in MDS.

Double Strand Break Repair

DNA double strand breaks (DSBs) are the most important class of DNA damage because, if unrepaired, they can result in a loss of genetic material, chromosome abnormalities and possibly cell death. The two major mechanisms that repair DSBs are the homologous recombination and non-homologous end-joining pathways.

Non-homologous End Joining

Non homologous end joining (NHEJ) is active in all phases of the cell cycle and is considered to be the most important DSB repair pathway in mammalian cells. In

NHEJ the DSB is recognised by the Ku70/Ku80 heterodimer which then forms a complex with DNA-PKcs. Following recruitment of further proteins and DNA end processing, a XRCC4-ligase IV complex re-ligates the break. A number of patients have been reported who have a mutation in the ligase IV gene—Ligase IV syndrome—and bone marrow abnormalities, including MDS, are amongst the many clinical disorders (reviewed in Chistiakov et al. [17]).

Polymorphisms in NHEJ genes have been identified but have not been studied in either de novo MDS or t-AML/MDS. However a recent study found differences in the expression of several of the NHEJ proteins in MDS samples [22]. Expression of ligase 4 was significantly elevated in MDS bone marrow samples compared to control bone marrow with the high expression appearing to be associated with a good risk karyotype. Conversely, the Ku70 protein levels were significantly lower in patients with a good risk karyotype.

Homologous Recombination

Homologous recombination (HR) repair is a tightly regulated, high-fidelity process. It uses a second, intact copy of the chromosome as a template to copy the information lost at the DSB site. A number of polymorphic genes involved in the pathway have been studied in the context of MDS.

RAD51 and XRCC3

RAD51 is a central protein in the HR repair pathway binding to DNA and promoting ATP-dependent homologous pairing and strand transfer reactions. XRCC3 also participates in the pathway interacting with, and stabilising, RAD51. Polymorphisms are present in the RAD51 and XRCC3 genes.

RAD51 has a G to C polymorphism at position −135 of the 5′ promoter of the gene [83]. Characterisation of the RAD51 promoter demonstrated that the −135 variant C allele was associated with increased promoter activity [29]. However, a further study suggested that the effect of the polymorphism was due to alternative splicing within the RAD51 5′-untranslated region [4]. The substitution of C for G abolishes a splice site resulting in low transcript levels of the longer RAD51 isoform (isoform 2). The authors suggested that as isoform 2 lacks a translation-inhibitory GC-rich region then it would be expected to have increased translation efficiency. As the polymorphic variant results in less isoform 2, subsequently, a reduction in RAD51 protein may occur.

The XRCC3 gene is also polymorphic and a thr to met substitution occurs at codon 241 [72]. Whilst the variant protein has been shown to complement the DNA repair defect in a XRCC3-deficient cell line [5], further work determined that the variant protein was unable to apoptotically eliminate aberrant cells with mitotic defects resulting in genetic instability [45].

Two studies have found no differences in the distribution of the RAD51-G135C and XRCC3-thr241met polymorphisms in MDS samples compared to controls

[10, 23]. Baumann et al. also found no difference if the two polymorphisms were analysed in combination. In t-AML/MDS we found an over-representation of the RAD51-135C allele when compared with a control group (OR 2.66, 95% CI 1.17–6.02, p = 0.02) [69]. Whilst there was no difference in the distribution of the XRCC3 polymorphism, when we looked at the combination of variant RAD51 and XRCC3 alleles we found a prominent synergistic effect resulting in an odds ratio of more than 8 (OR 8.11, 95% CI 2.22–29.68, p = 0.002).

BLM, TOP3A and RMI1

Bloom syndrome is a rare autosomal recessive disorder characterised by growth retardation, sensitivity to light and a predisposition to the development of many cancers including leukaemia and MDS. BLM is a RecQ helicase which prevents illegitimate recombination in mitotic cells. The BLM gene is mutated in Bloom syndrome resulting in an elevated frequency of exchange between homologous chromosomes and sister chromatids. BLM interacts physically and functionally with both topoisomerase IIIa (TOP3A) and RMI1/BLAP75 (reviewed in [75]. Polymorphisms in BLM, RMI1 and TOP3A have been studied in MDS.

RMI1 harbours a G to A polymorphism which results in a ser to asn change at codon 455 of the protein. Ser455 is evolutionarily conserved however the functional consequences of the polymorphism are unknown [13]. The presence of the polymorphic asn residue was demonstrated to be a risk factor for MDS (OR 1.9, 95% CI 1.1–3.3) [13]. Interestingly the effect was stronger in those patients over the age of 65 years which the authors suggested may reflect the fact that mitotic recombination increases with age and aberrations of proteins involved in this process may therefore be expected to have an increased influence as mitotic recombination increases. A second study by the same group examined a further 26 polymorphisms in RMI1, BLM and TOP3A in a mixed group of MDS and AML samples (37% MDS; 12% AML secondary to MDS; 51% AML). Of particular attention when analysed singly were TOP3A GA rs12945597 where the homozygous variant was associated with a 4.6-fold increase risk of MDS/AML (95% CI 1.7–14) and BLM AC rs6496724 for which the variant homozygote was less frequent in MDS/AML (OR 0.34, 95% CI 0.12–0.95) [14]. Following analyses of multiple myeloma, bladder and breast cancer samples in addition to the MDS/AML cohort, combinations of polymorphisms were chosen. The TOP3A rs12945597 A allele in combination with the BLM rs2532105 variant T allele resulted in an odds ratio of 2.4 for MDS/AML risk (95% CI 1.1–5.4). None of the functional effects of the polymorphisms, if any, are known.

Base Excision Repair: hOGG1

The base excision repair (BER) pathway corrects individually damaged bases which can occur via a number of different mechanisms but predominantly via

oxidation. The major product of oxidative damage to DNA is 8-oxoG. 8-oxoG is highly mutagenic as it has a tendency to mispair with adenine thereby generating GC to TA transversions. The human glycosylase responsible for repairing this base adduct is hOGG1 (reviewed in Klungland and Bjelland [36]). A SNP exists at position 1,245 of the hOGG1 gene resulting in a ser to cys amino acid change at codon 326 in exon 7 of the corresponding protein. The cys-encoding protein has been shown to have a reduction in its repair activity compared to the wild type ser protein [38]. Jankowska et al. have provided a comprehensive analysis of the importance of 8-oxoG in MDS including the genotyping of 146 MDS patients for the hOGG1 ser326cys polymorphism [33]. When comparing the distribution of the hOGG1 SNP in MDS to that of a cohort of 350 controls, significantly increased risks for MDS were found for both heterozygote (OR 1.7, 95% CI 1.1–2.5, $p = 0.02$) and homozygote cases (OR 2.8, 95% CI 1–7.2, $p = 0.05$). The cys allele was associated with conferring a particularly strong risk for advanced MDS and additionally there was a significant positive relationship between the presence of the cys allele and the frequency of chromosomal abnormalities ($p < 0.02$). The authors also compared hOGG1 mRNA expression between the different hOGG1 genotype groups with the carriers of hOGG1-cys326 exhibiting significantly higher hOGG1 levels when compared to the wild type hOGG1 ser/ser cases ($p = 0.008$). They suggested that this could be due to a feedback mechanism attempting to compensate for the reduced activity of the cys allele.

XRCC1 also participates in the BER pathway acting as a scaffold and recruiting other BER proteins to the repair site. A common variation in the gene substitutes arg for met at position 399 of the protein, a region which comprises the BRCT domain [72]. The variant Gln residue has been shown to result in significant conformational changes to the XRCC1 protein [50] and a large number of studies have shown that cells harbouring the variant gln allele have a decreased capacity to repair DNA damage resulting in increased DNA damage levels [8, 21, 41, 44, 47, 82, 84]. We have demonstrated that the presence of a variant XRCC1-399 gln allele was actually protective for t-AML/MDS (OR 0.44, 95% CI 0.20–0.93, $p = 0.03$) [68]. We consider this result indicates a strong gene-environmental interaction. The genotoxic therapy a patient receives for their primary condition is likely to cause very high DNA damage levels in some HSCs. Cells with reduced BER capacity, that is a XRCC1-399gln allele, are more likely to be driven towards apoptosis whilst the wild type cells may attempt repair but misrepair resulting in mutations and a clone which can initiate t-AML/MDS. This gene-environment (XRCC1-399gln: high DNA damage) hypothesis is supported by a study of XRCC1-399gln in non-melanoma skin cancer which is also associated with high levels of DNA damage; similar to t-AML/MDS a protective effect of the gln allele was found [54]. Furthermore in a meta-analysis of XRCC1-399 in smoking-related cancers, the variant gln allele was found to confer an increased risk in light smokers, but was protective among heavy smokers who presumably have high levels of DNA damage [31].

Nucleotide Excision Repair

Whereas BER removes the products of minor structural base damages, nucleotide excision repair (NER) removes bulky damages which distort the DNA helix. The NER repair pathway consists of removing segments of ssDNA containing the bulky lesion followed by repair synthesis by a DNA polymerase and ligation. Kuramoto et al. measured the mRNA expression levels of several genes involved in the NER pathway, namely ERCC1, ERCC3, ERCC5 and XPC, and found a reduction in expression in at least one gene in more than 20% of the MDS samples when compared to normal samples. Additionally, patients with high risk MDS were more likely to have a reduction in NER gene expression [42]. The authors suggested that such a decrease in DNA repair gene expression may predispose individuals to chromosomal instability and underlie the pathophysiology of the disease.

The ERCC2 (XPD) gene harbours a lys to gln change at codon 751 [72]. Like many of the polymorphisms in DNA repair genes the functional consequences of the ERCC-751gln variant allele are still unclear and a review of the literature by Clarkson and Wood [18] questions whether a causal relationship between the ERCC2 gene and reduced DNA repair occurs; instead the SNP may be in linkage with another functional SNP. Whatever the consequences, the ERCC2-751gln homozygote variant has been associated with a significant increase of developing chemotherapy-induced t-AML/MDS (OR 2.22, 95% CI 1.04–4.74) [3].

Mismatch Repair

Mismatch repair (MMR) corrects mismatched DNA bases that can result from misincorporation errors that have avoided polymerase proof-reading activity during DNA replication. In addition MMR can also process some types of DNA damage. MMR is reasonably easy to study because deficiencies in the pathway result in an elevated rate of mutations which can be measured in simple repetitive DNA sequences (microsatellites). There have been a number of studies which have searched for MMR deficiency (microsatellite instability; MSI) in both de novo MDS and t-MDS/AML. A summary of the de novo MDS studies is shown in Table 2.2. Noteworthy is the study by Kaneko et al. (Table 2.2) because serial samples from the same patients were analysed demonstrating that MSI, when it occurs, is an early event and may then contribute to the pathogenesis of MDS.

There are also a large number of studies looking at the incidence of MSI in t-AML/MDS (reviewed in Seedhouse and Russell [67]). The incidence in the t-AML/MDS samples is much higher (approximately 50%) than for de novo MDS suggesting that a prerequisite of MSI in MDS is a significant burden of DNA damage. Along these lines is work done on the development of AML/MDS following azathioprine immunosuppressive treatment after organ transplant: Offman et al. proposed that AML/MDS development may reflect the selection and expansion of MMR-deficient clones within the bone marrow which are resistant to drug-induced damage. The lack of MMR is expected to lead to the accumulation of mutations

Table 2.2 Summary of microsatellite instability (MSI) studies in de novo MDS

Number of samples	Number of loci studied (up to)	% of samples with MSI[a]	Reference
6	4	33	[34]
19	10	16	[35]
9	22	11	[39]
12	12	8[b]	[71]
7	14	0	[12]
23	18	4[b]	[49]
29	10	0[b]	[48]
23	9	0[b]	[28]

[a] The proportion of loci showing MSI differs between studies.
[b] Results are shown for two or more loci displaying MSI and results indicate further samples have MSI at just one locus

which may subsequently result in a clonal haematopoietic disorder [58]. Further support of the importance of MMR in t-AML/MDS is a study showing that the variant allele of the MSH2 IVS12-6 T to C polymorphism [25] is over-represented in t-AML/MDS patients who had previously received alkylating therapy (OR 4.02, 95% CI 1.4–11.37) [88]. Strikingly both of the t-MDS/AML variant homozygotes had MSI, although not all of the MSI-positive samples had the polymorphism. The functional consequence of the polymorphism is unknown, although it resides in the splice acceptor site of exon 13 and may therefore alter splice site recognition.

Discussion

Protection from DNA damage, either by preventing (detoxification or apoptosis) or repairing it, is paramount in keeping our cells healthy and this is particularly so for haematopoietic stem and progenitor cells which often come into close proximity to damaging agents. An accumulation of unrepaired genomic damage in HSCs will results in an increased risk of a clonal stem cell disease. MDS is a disease characterised by DNA damage and genetic instability, a state that is expressed as gross karyotypic abnormalities in 50% of patients. Whilst many polymorphisms only have subtle functional effects, gene-environment interactions are likely to magnify these effects making polymorphisms worthwhile of study. We are now accumulating evidence demonstrating a contribution of polymorphisms in detoxification pathways and DNA repair pathways to MDS susceptibility, however there is still more work to be done.

Sample Size and Controls for Polymorphism Studies

Much of the work on susceptibility to MDS has focused on polymorphisms in the DNA repair and detoxification genes. Many of the polymorphic genes have only been investigated in single small studies, whilst those polymorphisms which have

been assessed by more than one group have produced contradictory results. The answer in improving this body of work is by increasing sample sizes; very large cohorts of well characterised MDS patients are needed. In this respect we are participating in a large European study in which we have already collected more than 1,000 MDS samples and determined the genotypes at a number of polymorphic sites.

Many sources of control samples have been used in the studies described herein. Appropriately matched controls, whilst often not easy to obtain, are an absolute requirement for epidemiological studies. However, we also consider it important to compare subgroups within MDS and suggest that this will help improve our knowledge on understanding MDS genetic susceptibility. For example are some polymorphic variants more prevalent in high risk MDS? Or does a particular polymorphism confer risk to a specific cytogenetic abnormality such as the GSTT1 5q- story? There are many research avenues still to be followed.

Functional Consequences of Polymorphic Variants

A further caveat in polymorphism studies is the lack of data regarding their functional effects. Whilst many of the detoxification gene variants have been categorically shown to have reduced activity, for most of the DNA repair polymorphisms it is not known whether the sequence variant is functionally significant and more research into this question is required. The possibility of linkage disequilibrium between polymorphisms should also be considered.

Combinations of Polymorphisms

Another area of importance, only possible with very large studies, is the combination of variant genotypes. Detoxification and repair processes are complex and more than one protein/pathway can detoxify or repair a particular entity. This functional redundancy illustrates the critical importance of these processes and also poses the question of whether we are likely to see a noteworthy susceptibility to MDS if just one variant gene is studied. It is much more probable that MDS would result from the accumulation of minor phenotypic abnormalities caused by more than one variant protein. A few studies combining detoxification and repair genes have already been published in t-AML/MDS with the achievement of high odds ratios for the combinations [11, 69], although the number of samples was small. Once again, large sample sizes are required for adequate power for combination studies because the more polymorphisms combined the smaller the subgroups. High throughput genotyping techniques will aid this goal. We also suggest that such studies should be hypothesis-driven rather than a ‘fishing’ exercise where a lot of statistical tests upon a sample cohort are prone to a degree of false positivity. The hypothesis may take the form of aberrant detoxification genotypes with variant DNA repair genotypes of

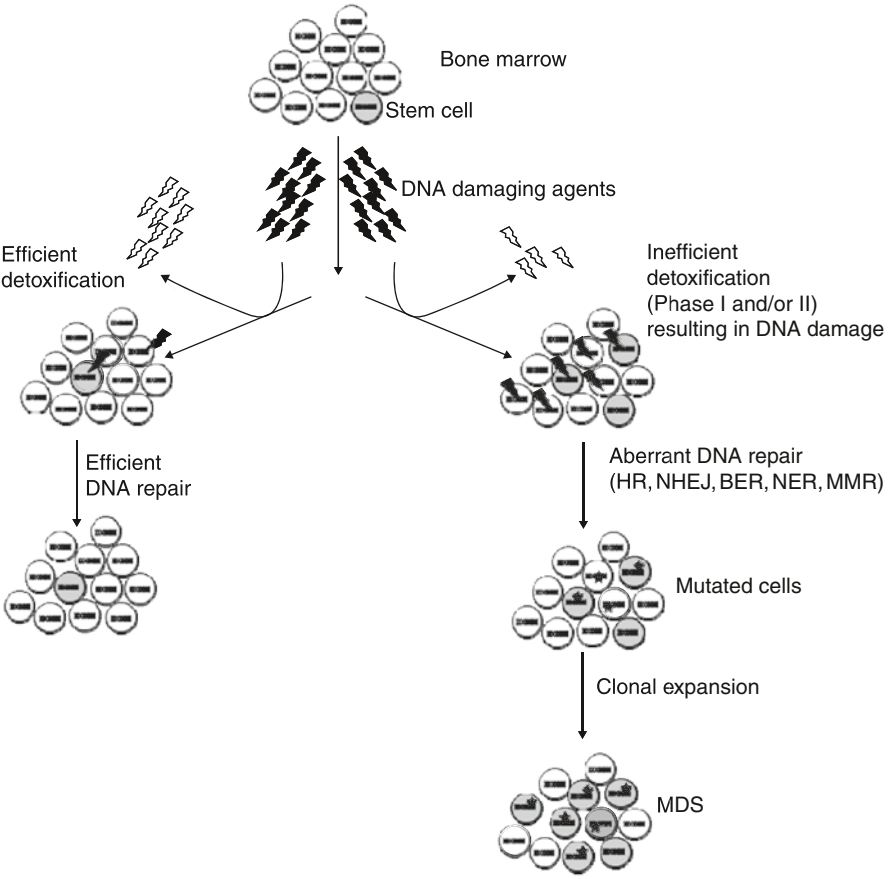

Fig. 2.1 Pathway to MDS. Possible mechanism of increased susceptibility to MDS. Deficient detoxification mechanisms increase the amount of DNA damage which aberrant DNA repair mechanisms fail to repair. The resulting genetic instability may result in clonal expansion of mutated stem cells resulting in MDS

proteins expected to repair the particular damage resulting from the aberrant detoxification, or instead variants of more than one gene that are able to detoxify the same substrate or repair the same damage type (Fig. 2.1).

Which Polymorphic Genes Confer the Greatest Susceptibility to MDS?

We still do not know the answer to this question. Whilst GSTT1 appears to play a role and evidence is accumulating suggesting that members of the BLM complex may also be important, much of the data is contradictory and significant findings

often only generate odds ratios of between one and two. This is a long way from the relative risk factor of ten suggested by Knudsen et al. [37] as a safety factor to allow for individual susceptibility. We are of the opinion that we are unlikely to find high risks associated with single gene studies but that the study of more than one gene from the detoxification/DNA repair pathways would be more successful. Hopefully larger studies and combination assessments will soon allow us to conclusively identify those genes which play the most important role in conferring susceptibility to MDS.

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