Mutational Signatures in Gastric Cancer

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Gastric cancer is characterised by high inter- and intratumour heterogeneity. The majority of patients are older than 65 years and the global burden of this disease is increasing due to the aging of the population. The disease is usually diagnosed at advanced stages, which is a consequence of nonspecific symptoms. A new field of mutational signatures has emerged in the past decade with advances in the genome sequencing technology. These distinct mutational patterns in the genome, caused by exogenous and endogenous mutational processes, can be associated with tumour aetiology and disease progression, and could provide novel perception on the treatment possibilities.

chromosomal instability | gastric cancer | genetic variability | gene expression | immune checkpoint inhibitors | microsatellite instability | mutational signatures

1. Introduction

In non-hereditary cancers the accumulation of somatic mutations in cells leads to clonal expansion and malignant transformation. Mutations occur in the genome due to exogenous and endogenous mutagens in the presence of normally or abnormally functioning DNA maintenance machinery. The ones that occur in critical genes, which maintain cell integrity and result in cell growth advantages, are known as “driver” mutations. At the same time many other mutations accumulate in the genome regions with no result in functional or phenotypic change, so-called “passenger” mutations. Each exo- and endogenous mutational process leaves a distinct mutational pattern of both driver and passenger mutations on the genome - termed “mutational signature” (in some publications the term mutational fingerprint is used) [1]. Mutational signatures are correlated to specific endo- or exogenous mutagenic processes, such as spontaneous deamination of CT due to aging, overactivity of APOBEC cytidine deaminase enzymes, defects in DNA repair machinery, tobacco smoking and so on. Some mutational signatures are rare and specific, whereas other are more common and can be detected in most cancer types, such as mutational signatures resulting from reactive oxygen species (ROS), APOBEC overactivity and defective mismatch repair (MMR) [2]. The underlying mechanisms remain unknown for many mutational signatures and further *in vitro* experiments on cell lines, exposed to mutagenic processes in defined environments, are necessary to decode the causal mutagenic factors. Gastric cancer falls into the category of cancer types with a complex repertoire of mutational processes. This discussion includes WES and WGS mutational signatures found in 75 samples from gastric adenocarcinoma tumours by Alexandrov et al., which are also described in the COSMIC database [2][3] and their possible implications in gastric cancer prevention, diagnosis, and treatment (**Table 1** and **Figure 1**).

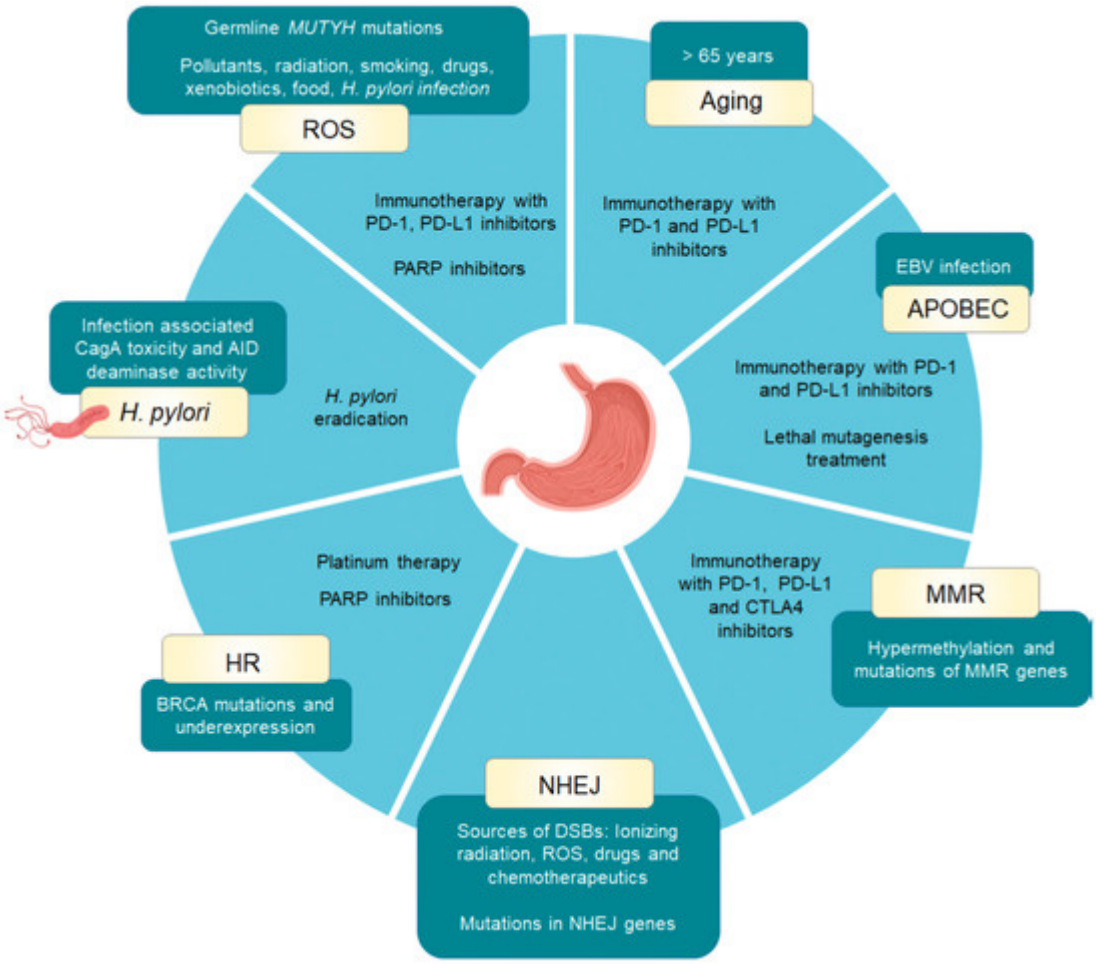

Figure 1. Risk factors and current treatment possibilities associated with gastric cancer mutational signatures. Mutational signatures found in gastric cancer are represented in yellow boxes. Corresponding risk factors are represented in green boxes and current treatment possibilities are listed in the circle diagram. For NHEJ inhibition, no treatment options are currently in clinical use. HR, homologous recombination; MMR, mismatch repair: NHEJ, nonhomologous end joining; ROS, reactive oxygen species. Illustrations created with BioRender.com.

Table 1. Summary of mutational signatures in gastric cancer and their potential treatment implications.

Underlying Mechanism	Signature Type: Base Substitution Subtype [1] [References]	Molecular Consequences	Treatment Implications [References]	Additional Biomarkers [References]
Aging	SBS1: C > T (N**C**G) [4][2][5][6]	Deamination of 5-methylcytosine	**immune checkpoint inhibition (PD-L1 and PD-1 inhibitors)** [7][8][9]	senescence score, **EBV$^+$**, **TMB** [10]
APOBEC overactivity	SBS2: C > T (T**C**N) SBS13: C > A (T**C**A), C	High mutational load in transcriptionally active genes	APOBEC3B inhibitors, immune	**EBV$^+$**, **TMB**, L1-sequencing, APOBEC3B

Underlying Mechanism	Signature Type: Base Substitution Subtype [1] [References]	Molecular Consequences	Treatment Implications [References]	Additional Biomarkers [References]
	> G (T**C**A, T**C**C, T**C**T) [4][2][11][12][13][14]		checkpoint inhibition (PD-L1 and PD-1 inhibitors), lethal mutagenesis treatment [15][16][17][18]	expression levels [2][12][17][19]
Homologous recombination repair (*BRCA1/2* mutations)	SBS3: C > A, C > G, C > T, T > A, T > C, T > G (N**N**N) [3] ID6: microhomology—deletion length: 5+ (microhomology length: 1, 2, 3, 4, 5+) [19][4][20]	Higher mutational burden due to alternative error-prone DSBs repair by NHEJ	**Pt-based therapy**, **PARP inhibitors** [21][22][23][24]	**BRCA1/2 expression levels,** *ATM* loss [25][26][27]
Mismatch repair	SBS20 (*POLD1* mutations): C > A (C**C**C, C**C**T), C > T (A**C**A, G**C**A, G**C**C) SBS6, SBS14 (*POLE* mutations), SBS15, SBS21, SBS26, SBS44 [2] DBS7: AC > NN (CA), CT > NN (TC), GC > NN (AT), TA > NN (AT), TT > NN (AA, AG, CA, GA) DBS10: CG > NN (TA), TT > NN (GG) ID1: 1 bp insertion (T, homopolymer length: 5+) ID2: 1 bp deletion (C, homopolymer length: 5, 6+) [2][28]	Microsatellite instability, middle to high tumour mutational burden	**Immune checkpoint inhibition (PD-L1, PD-1 and CTLA4 inhibitors)** [29][30][31][32][33][34]	**MMR mutations**, **MSI status**, **PD-L1 status**, **EBV$^+$**, **T-cell inflamed score**, **TMB status,** *POLD1* mutations, *ARID1A* mutations [35][36][37][38][39][40]
Nonhomologous end joining repair	ID6: microhomology—deletion length: 5+ (microhomology length: 1, 2, 3, 4, 5+) ID8: > 1 bp deletion at repeats—deletion length: 5+ (number of	Chromosomal instability	NHEJ inhibitors [41][42][43]	CIN, KUs, DNA-PKcs, DNA ligase IV, XRCC4 expression levels [35][40]

Underlying Mechanism	Signature Type: Base Substitution Subtype [1] [References]	Molecular Consequences	Treatment Implications [References]	Additional Biomarkers [References]
	repeat units: 1); microhomology—deletion length: 5+ (microhomology length: 1, 2, 3) [2]			
Reactive oxygen species DNA damage	SBS18: C > A (A**C**A, C**C**A, G**C**A, G**C**T, T**C**A, T**C**C, T**C**T) [2][44]	DNA damage	**Immune checkpoint inhibition therapy (PD-L1 and PD-1 inhibitors) PARP inhibitors** [45][46][46]	MUTYH mutations and expression levels, *CHEK1* mutations [44][47][48][49]
[5][6] *H. pylori* infection	SBS3: C > A, C > G, C > T, T > A, T > C, T > G (N**N**N) [3] ID6: microhomology—deletion length: 5+ (microhomology length: 1, 2, 3, 4, 5+) [2][20][50]	Inflammation, DNA damage	***H. pylori* eradication** [4][52]	AID expression levels [51]

al cells [2]. issues at related to ted base or cytidine smatches, t cytosine [53]. Uracil is readily repaired in cells with functional uracyl-DNA glycosylase and base excision repair, whereas T:G base pairing is recognised by thymidine-DNA glycosylase. Evidence showed that T:G mismatches, particularly in the context of CpG islands, are often associated with mutational hotspots in certain genes, such as *TP53* [54]. Interestingly, when comparing signature SBS1 mutation rates between different tissue types, they were the highest in stomach (23.7 mutations per gigabase per year) followed by colorectum (23.4 mutations per gigabase per year), whereas the rates were the lowest in breast tissues (3.1–3.9 mutations per gigabase per year) [6]. This is attributed to high mitotic rates of gastric and colon epithelia, where cells completely turnover every 2–7 days under physiological conditions [55]. Although this is a universal signature that may be correlated with the age of the patient and perhaps to some extent with the mitotic rate of tissue of origin, it could still be clinically relevant in combination with other markers of senescence. It could perhaps be included in the senescence scoring models, with potential prognostic values. Zhou et al. constructed a senescence scoring system based on six genes (*ADH1B*, *IL1A*, *SERPINE1*, *SPARC*, *EZH2*, and *TNFAIP2*) and showed that patients with high senescence score (senoscore) had longer overall survival (19.6 months vs. 56.2 months; $p < 0.0001$) [10]. Furthermore, when patients were stratified according to TNM (tumour node metastasis) clinical stages, the senescore successfully separated patients with distinct clinical prognosis at the same disease stage. High senoscore was also related to the MSI-high status, Epstein–Barr virus (EBV) infection, and higher TMB, suggesting that these patients would benefit from immune checkpoint inhibitors, such as PD-1 and PD-L1 [7][8][9]. It has been observed that patients with high senoscore may experience stronger adverse effects after chemotherapy and cancer relapse [56]. Therefore, research results suggested that patients with low senoscore would be better candidates for chemotherapy.

[1] Only base substitutions with more than 5% of percentage of single base substitutions or indels (ID) with more than 5% of percentage or DBS with more than 5% of doublet base substitutions. [2] These SBS mutational signatures are presented in **Table 2**. [3] All substitutions in all contexts are below 2.5% of percentage of single base substitutions. Treatment options and biomarkers already implemented in clinical use for cancer treatment and diagnosis/prognosis are in bold. CIN: chromosomal instability; EBV: Epstein–Barr virus; L1: retrotransposon element; MMR: mismatch repair; MSI: microsatellite instability; N: any base; TMB: tumour mutational burden.

3. APOBEC Activity

SBS2 and SBS13 mutational signatures are found in more than half of all cancer types including gastric cancer and are ranked second in cancer mutagenesis, with aging being the first one [4]. They are associated with the activity of the activation-induced cytidine deaminase/apolipoprotein B editing complex (AID/APOBEC) enzyme family. Signature DBS11 is also found in samples with a large number of SBS2 and SBS13 mutations, although it has been correlated with ROS based on experiments in bacterial models [11]. The AID/APOBEC family comprises eleven members with distinct functions. These enzymes deaminate cytidine to uridine in the DNA and/or RNA, and are implicated in adaptive (antibody gene diversification) and innate immunity (virus restriction) as well as in retrotransposon restriction. Their characteristics and functions have been reviewed in detail by Viera et al. and Conticello et al. [57][58]. A side effect of APOBEC overexpression is off-target genomic mutations, which accumulate in the host DNA, affect the DNA integrity, and lead to neoplastic transformation. APOBEC mutational signature is characterized by C > T transition mutations (SBS2) in DNA motifs TpCpW and C > G transversions in SBS13 in TCW DNA motifs (mutated base underlined; W = A or T), and other mutational outcomes that occur due to DNA repair intermediates such as abasic sites and DNA breaks [59]. The substitutions occur during replication of uracils formed by APOBEC cytidine deamination and by error-prone polymerases following uracil excision and generation of abasic sites by uracil–DNA glycosylase [60][61].

In viral infections, APOBEC mutates viral ssDNA/ssRNA in order to hamper virus replication and function [57]. Viral infections are associated with the development of a number of cancers. Hepatitis B virus (HBV) is one of the leading causes of liver cancer; human papilloma virus (HPV) causes anal, cervical, penile, oropharyngeal, vaginal, and vulvar cancer; human T-lymphotropic virus type 1 (HTLV-1) is associated with adult T-cell leukemia/lymphoma; hepatitis C virus (HCV) with liver cancer and non-Hodgkin's lymphoma; and EBV with the risk of Burkitt lymphoma, some types of Hodgkin's and non-Hodgkin's lymphoma, and, importantly, gastric cancer. According to the TCGA study on 295 primary gastric adenocarcinoma samples, around 8.8% were characterised as EBV positive (EBV^+) with distinct molecular characteristics—mutations in *PIK3CA* and *ARDN1A*, DNA hypermethylation, overexpression of PD-L1/2, amplification of *ERBB2* and *JAK2*, low rate of *TP53* mutations, and intestinal subtype [35]. In addition, strong IL-12 signalling indicated that EBV^+ tumours were infiltrated with immune cells. In the ACRG study, using different approaches to molecularly stratify gastric cancer subtypes, the researchers observed that EBV infection occurred more frequently in the MSS/$TP53^+$ group (n = 12/18 of EBV^+) [62]. Overall, in their cohort, 6.5% samples were characterised as EBV^+. They also observed frequent *PIK3CA* and *ARDN1A* mutations and a distinct cytokine signature, indicative of increased infiltration of immune cells in EBV^+ tumours compared to microsatellite stable (MSS) tumours. The predominant histology of tumours in this group was also intestinal-type carcinoma. They did not observe alterations in *TP53*, which is partly consistent with the finding from the TCGA study, where the majority of EBV^+ tumours had intact *TP53*. Interestingly, in the ACRG study, *MDM2* was amplified in MSS/$TP53^+$ cancers, whereas in the TCGA study it was not.

Bobrovnitchaia *et al.* analysed 240 gastric cancer samples from the TCGA cohort and 112 samples from a different Brazilian validation cohort and showed that the expression of *APOBEC* genes was significantly higher in EBV^+ tumours in comparison to EBV^- tumour samples [22]. With the exception of *APOBEC3A*, all other members of the

*APOBEC3*s were upregulated, with *APOBEC3C* being the most abundantly expressed. The authors also showed that *APOBEC* characteristic TpCpW mutation pattern was significantly enriched in EBV^+ group and positively correlated with *APOBEC3* expression, which further correlated with tumour purity, suggesting that APOBEC activity derives from tumour cells. APOBEC mutational load correlated with highly expressed genes, which were, as expected highly mutated. This is in concordance with the fact that the preferential editing substrate of APOBEC3s is ssDNA, which is available at transcriptionally active sites. The authors also observed enrichment of TpCpW mutations in the late-stage EBV^+ tumours, which also carried higher proportion of mutated oncogenes in comparison to EBV^- samples. Furthermore, in 40% of EBV^+ patients with somatic mutations in PIK3CA, mutations were present in TpCpW motif, while this was not observed in EBV^- patients.

Higher expression patterns of mRNA and protein levels of APOBEC3B were also found in gastric cancer tumour samples compared to paired normal tissue samples in a cohort of 236 patients [56]. *APOBEC3B* mRNA and protein levels were higher in tumour samples from Grade III stage in comparison to Grade I or Grade II stage and correlated to poor prognosis. High *APOBEC3B* expression was also associated with gender (female), tumour size (> 5.0 cm), histological grade (G3), and TNM staging (lower expression in TNM I). *APOBEC3B* down-regulation with shRNA resulted in enhanced cytotoxicity of PDCD2 (Programmed cell death protein 2) in gastric cancer cell line MKN28, probably due to the lower mutational load and non-interfered transcription of this tumour suppressor gene. *APOBEC3B* expression levels were associated with APOBEC mutational signatures, whereas *APOBEC3C* expression levels were associated with decreased APOBEC mutational signatures in gastric cancer [23].

Interestingly, analysis of cancer cell lines by sequencing single cells showed that at least 75% of investigated cancer cell lines (including gastric cancer) that previously encountered APOBEC mutagenesis persistently continued to generateSBS2 and SBS13 mutational signatures [25]. The authors suggested that APOBEC-associated mutagenesis *in vivo* appears to be episodic. Additionally, the procurement of APOBEC-associated mutational signatures continued in cell culture despite the absence of proposed initiators of APOBEC activity, immune system and exogenous viral infections [17][26]. Indeed, the presence of a virus is not necessarily required for initiating APOBEC mutagenesis [25]. This may occur also due to retrotransposition activities. There was significant correlation between the rates of the *in vitro*-acquired retrotransposition aberrations and burdens of SBS13 and, interestingly, SBS18 (associated to ROS) shown in cancer cell lines. However, the correlation was not significant when 2,353 primary cancers originating from different tissues were investigated. L1s are autonomous mobile elements, amounting to 17% of the human genome, and retrotranspose via an RNA intermediate through a “copy and paste” mechanism [27]. Somatic mobilization of retroelements can induce and accelerate insertional mutagenesis and genetic instability. Next-generation L1-resequencing (L1-seq) on paired tissue samples from seven patients with primary gastric cancer showed that somatic retrotransposition was present early in cancer development in gastro-intestinal epithelial cells [28]. L1-seq, APOBEC-mutational signature, and APOBEC-expression status in stomach tissues in combination with circulating biomarkers could therefore be valuable as biomarkers for early detection of gastric cancer.

Tumours characterized by APOBEC overactivity might be candidates for treatment by lethal mutagenesis [29]. Drugs, such as nucleoside analogues that increase the mutation load in tumour cells to toxic levels are already

commonly used in addition to platinum-based chemotherapy to destroy tumour cells. On the other hand, inhibition of APOBEC enzymes may prevent cancer evolution. APOBEC3B specific inhibitors are promising, as this enzyme is non-essential in humans, whereas other members of the family are crucial for adaptive (AID) and innate (other APOBEC members) immune response [30]. Drug candidates for such “therapy by hypomutation” are being pursued. In recent years many studies of APOBEC3B crystal structures were published providing better understanding of APOBEC3B active site dynamics and setting the stage for design of selective small molecule inhibitors [31][32][33]. These may in the future in combination with other therapies be effective in preventing tumour recurrence and drug resistance.

Furthermore, a study by Wang and Jia *et al.* suggested that APOBEC3B and APOBEC-mutational signature might be a novel marker for predicting immunotherapy response [34]. They found a correlation between *APOBEC3B* expression and immune gene expression and known immunotherapy response biomarkers in patients with non-small cell lung cancer. APOBEC mutational signature was specifically enriched in patients with lasting clinical benefit after immunotherapy, suggesting that patients with APOBEC signatures might be candidates for checkpoint blockade immunotherapy with PD-1 and PD-L1 (discussed in detail in section 3.3.2). Similarly, Boichard and Pham *et al.* demonstrated that APOBEC related mutagenesis could be correlated with immunotherapy response in patients with various cancer types (gastric cancer excluded) [36].

All the factors, responsible for the expression of AID/APOBEC enzyme family are currently unknown. Nevertheless, altogether this data suggest that it might be worth analysing the presence of APOBEC mutational signature and the expression levels of APOBEC enzymes in gastric cancer biopsies as they can be a source of ongoing mutagenesis at transcriptionally active DNA sites or retrotranspozable elements providing a secondary driving force for subclonal expansions and intratumor heterogeneity propagation. This may manifest clinically as recurrence, metastasis, and drug resistance and could therefore have important prognostic and therapeutic implications. In a cohort analysed by Alexandrov *et al.* APOBEC signatures were present in < 50% of all gastric cancer samples indicating that this feature was not common for all gastric adenocarcinoma tumours and could therefore be useful for patient stratification in combination with other markers, such as PD-L1 positivity, TMB, and EBV infection status [2].

4. DNA Integrity Machinery

Compromised DNA replication and repair mechanisms play a central role in cancer development. Deficient DNA integrity machinery leaves distinct imprints in the genome. Therefore, it is no surprise that several mutational signatures were associated with aberrations of specific DNA repair mechanism or a specific DNA repair gene [2]. Inhibitors of compromised DNA repair pathways are promising drugs for cancer treatment and could be used as monotherapy or in combination with first-line chemotherapeutics to increase tumour mutational burden. However, it is difficult to select the patients who would benefit from a particular combination therapy due to the lack of specific biomarkers. Mutational signatures could be a promising tool for filling the gap in biomarker selection for better patient stratification in gastric cancer.

4.1. Homologous Recombination DNA Repair

SBS3 was associated with germline or somatic mutations in *BRCA1* and *BRCA2,* and *BRCA1* promoter methylation [19][4]. BRCA1/2 tumour suppressors play an important role in the response to DNA damage, particularly DNA double-strand breaks (DSBs), which are usually repaired by error-free homologous recombination repair (HRR) [63]. Additionally, they maintain genome integrity by chromatin remodelling, and transcriptional and cell cycle regulation . Defects in BRCA1/2 lead to activation of alternative error-prone DNA repair mechanism by nonhomologous end joining (NHEJ) [64]. Consequently, cells have higher mutational burden, which in time leads to neoplastic transformation. *BRCA1/2*-associated mutational signature is commonly accompanied by small deletions with overlapping microhomology at their boundaries (specified as ID6) and large numbers of rearrangements, such as tandem duplications (short tandem duplications (1–10 kb)) and (longer tandem duplications (>100 kb)) as well as indels (deletions (1–10 kb)) [19][65][66]. SBS3 is very common in breast, ovarian, and pancreatic cancer with mutations in *BRCA1/2* genes; however, it is also present to a smaller extent in other cancer types with no mutations in *BRCA1/2* or other genes involved in double-strand break repair [2].

Alexandrov et al. analysed the data from 372 whole-exome and 100 whole genome sequences from gastric cancer patients and showed that SBS3 is present in 7.3% of the examined whole-exome and in 12.0% of the examined whole-genome gastric samples [20]. Samples with SBS3 had statistically significant elevation in large indels with overlapping microhomologies and structural rearrangements, and were enriched in the intestinal type by Lauren's classification. Interestingly, although some gastric samples harboured *BRCA1* or *BRCA2* somatic mutations, they were not enriched with SBS3, suggesting that these mutations may actually derive from defective MMR.

The researchers suggested that gastric cancer patients with SBS3 might benefit from platinum therapy or PARP inhibitor treatment since this approach was beneficial in breast, ovarian, prostate, primary peritoneal, and pancreatic cancers with defective DSB repair due to BRCA1/2 mutations, HR mutations, or high genomic instability score [20]. Platinum–DNA adducts are genotoxic and BRCA1/2-defective neoplastic cells undergo apoptosis as DNA damage accumulates and cannot be efficiently repaired. PARP inhibitors mediate selective cytotoxicity as they introduce even more DSBs in tumour cells with deficient HRR by inhibiting PARP1, responsible for single-strand break repair. When these remain unrepaired, DSBs are formed during DNA replication. It has been established that breast and ovarian cancers with defective BRCA1/2 benefit from treatment with a range of PARP inhibitors [21][22]. In addition, a study on WGS data from pancreatic cancer samples revealed that patients with SBS3 responded to platinum therapy [24]. Recently, this approach has also been proven successful for small cell lung cancer [23].

There is an ongoing debate about non-BRCA-mutant tumours, which exhibit BRCAness and HRR deficiency, and their sensitivity to PARP inhibitors [22]. Patient stratification based on the presence of SBS3 mutational signature and accompanying indels and rearrangements as a biomarker would perhaps be more effective and would provide additional information to BRCA1/2 mutational/expression status. Further large studies that would examine the benefit of platinum and PARP inhibitor treatments in gastric cancer patients with SBS3 in addition to other biomarkers are necessary to confirm this association.

4.2. DNA Mismatch Repair Deficiency

SBS6, SBS14, SBS15, SBS20, SBS21, SBS26, and SBS44 were strongly associated with deficient MMR and microsatellite instability [2]. The common characteristics of these mutational signatures are presented in **Table 2**. Interestingly, the majority of patients with gastric cancer were characterised by SBS15 (60/486) and SBS20 (56/486), followed by SBS44 (17/486), SBS26 (11/486), SBS6 (9/486), and SBS21 (5/486). SBS14, which was associated with *POLE* mutations in addition to MMR deficiency, was found in only one gastric cancer sample (1/486). All mutational signatures were strongly associated with ID1 and ID2 [3]. The SBS profiles and the additional data on the transcriptional and replicational strand symmetry could either be the consequence of sequencing artefacts or it could reflect chemotherapy or carcinogen exposure, or could also indicate the underlying biological mechanisms leading to specific mutation profile. Therefore, distinct mechanisms could contribute to the differences in base substitutions. In particular, SBS20 was conjoined with mutations in *POLD1* and was characterised mainly by C > A substitutions in CpCpT and CpCpC and less by C > T substitutions (discussed in more detail in the next section). This is in contrast with SBS15, which is distinguished predominantly by C > T substitutions in the GpCpN context. Next, indications that some substitutions are asymmetrically distributed between leading and lagging strand and between transcribed and untranscribed strand could lead future research to identify aberrations in cell processes, implicated in this specific mutator phenotype [2][3]. Approximately 22% of examined tumours in the TCGA study and ACRG study were classified as microsatellite unstable (MSI) tumours, displaying numerous mutations in receptor tyrosine kinase (RTK) and RAS signalling pathways (*EGFR*, *ERBB2*, *ERBB3*, *JAK2*/*PD-L1*/*2*, *FGFR2*, *MET*, *VEGFA*, *KRAS*/*NRAS*, *RASA1*) and in the PI(3)-kinase pathway (*PIK3CA* and *PIK3R1*) and frequent truncating mutations in *PIK3R1* and *PTEN* [35][62]. Therefore, activation of different cell processes, such as promoting cell division and/or transcription, could in combination with other accumulated aberrations result in the observed asymmetry of mutational signatures on the DNA strands.

Table 2. Characteristics of MMR-associated mutational signatures.

SBS	Base Substitution Subtype [1]	Associated ID	Transcriptional (T) and Replicational (R) Strand Asymmetry in Stomach Cancer
SBS6	C > T (ACA, ACG, CCG, GCN)	ID1, ID2	T:/ R:/
SBS14	C > A (ACT, CCT, GCT, TCT)	ID1, ID2	T:/ R:/
SBS15	C > A (CCA) C > T (ACG, GCN)	ID1, ID2	T:/ R:/
SBS20 [2]	C > A (CCC, CCT) C > T (ACA, GCA, GCC)	ID1, ID2	T: no significance R: lagging, C > A
SBS21	T > C (GTN, TTA, TTC, TTT)	ID1, ID2	T: no significance R: lagging strand, T > C
SBS26	T > C (ATA, ATC, CTA, CTG, CTT, GTA,	ID1, ID2	T: untranscribed strand, T > C R: lagging strand, T > C

SBS	Base Substitution Subtype [1]	Associated ID	Transcriptional (T) and Replicational (R) Strand Asymmetry in Stomach Cancer
	GTG, GTT, TTT)		
SBS44	C > A (CCT) C > T (ACA, GCN)	ID1, ID2	T: no significance R: lagging strand, C > A; leading strand, C > T and T > A

[1] Only base substitutions with more than 5% of percentage of single base substitutions. [2] Characterised by *POLD1* mutations.

The main mechanism contributing to MSI phenotype in sporadic gastric cancers is hypermethylation of *MLH1* promoter [35]. MSI phenotype in gastric cancer has favourable prognosis, particularly for women; however, analysis of several clinical trials (MAGIC, CLASSIC, ARTIST, and ITACA-S) indicated that high MSI status (MSI-high) was negatively associated with the efficacy of adjuvant or neoadjuvant chemotherapy in gastric cancer patients [35][40]. Interestingly, some of the MSI tumours also harboured frequent common alterations in major histocompatibility complex class I (*MHC I*) genes, suggesting that alterations in *MHC I* genes, which play a crucial role in antigen presentation, could contribute to tumour evasion from the immune response. It has been postulated that this subset of patients could benefit from immune-based therapies [35][67]. Several studies of different cancer types showed that high tumour mutational burden, MSI, and PD-1/PD-L1 immunohistochemical status in tumour tissues could identify patients who would respond to immune checkpoint inhibitors (ICIs). ICIs have emerged as a promising new treatment option for gastric cancer patients as well, improving the 12-month and 18-month overall survival (RR, 1.79 $p = 0.013$; 2.20 $p = 0.011$) in patients with advanced and metastatic stomach adenocarcinomas [29][30][31].

Immunotherapy, targeting immune checkpoints, has been approved for MMR-deficient and MSI gastric tumours; however, conflicting reports regarding the effectiveness of this therapy have been observed, ranging from only 10–20% or up to 60% of gastric cancer patients responding favourably to ICIs [32][33][34]. In addition, a subset of patients showed worse prognosis after treatment [33][34]. Research efforts, focused on finding additional, more precise biomarkers that would better predict response to ICIs in addition to MSI/PD-1/PD-L1 status, have culminated in several new findings, such as the analysis of mutational burden in plasma-circulating tumour DNA (ctDNA), immune prognostic signatures, evaluation of the composition and ratios of immune cell subtypes, and so on [7][32][38][68][69][70]. Analyses of mutational signatures associated with deficient MMR and/or MSI could provide a deeper level in understanding the mechanisms of heterogeneity found among MSI-positive gastric cancers.

POLD1/*POLE* Mutations and MSI Phenotype

The SBS20 mutational signature, presented in COSMIC, was correlated with concurrent *POLD1* (DNA polymerase delta 1) mutations and defective DNA mismatch repair [3]. Interestingly, this is in contrast with the S4 signature, which was described previously and is similar to SBS20; however, mutations in *POLD1* were not characteristic for S4 [27]. SBS20 was associated with ID1 and ID2 and often found in the same samples as other microsatellite instability (MSI)-associated signatures SBS6, SBS14, SBS15, SBS21, SBS26, and SBS44 [3]. SBS20 was found using WES and WGS in 11.5% (56/486) samples of patients with gastric cancer [2]. POLD1 is a catalytic subunit of the DNA polymerase delta and possesses both 3′-5′ exonuclease activity and polymerase activity. It has a crucial role in high-fidelity genome replication, acting as major processive polymerase in lagging strand synthesis and probably minor polymerase in leading strand synthesis, assuming this role particularly during replication fork stress,

and in DNA resynthesis during DNA repair mechanisms, such as base excision repair, nucleotide excision repair, and homologous recombination repair [71][72][73][66]. Its damaging mutations affect genome integrity and stability and lead to accumulation of alterations in DNA, and tumour formation. The information on *POLD1*-associated mutational signature (SBS20) could therefore, in addition to other biomarkers such as MSI-high, indel-high, T-cell inflamed score-high, and PD-L1 positivity, prove valuable for identifying gastric cancer responders to ICIs [74][75][76][77][78].

A recent study that analysed mutations in *POLD* and *POLE* from the cancer patient cohort in cBioPortal observed high levels of *POLE/POLD1* mutations in several cancer types, including in 185 out of 2586 (7.2%) esophagogastric cancer samples [36]. They showed that cancer patients with *POLE*/*POLD1* mutations showed significantly longer overall survival in comparison to the wild-type population (34 vs. 18 months, $p = 0.04$), and that in addition to cancer type and MSI status, *POLE*/*POLD1* mutations were an independent risk factor for identification of patients who would benefit from ICI treatment. Similar results were observed in other studies for endometrial cancer, nonsmall cell lung cancer, and colorectal cancer, which also showed that patients with *POLD1* and *POLE* mutations might benefit from immunotherapy, more specifically ICIs, including antibodies targeting PD-1, PD-L1, or CTLA4 [79][80][81]. It should be noted that, interestingly, the number of cases with *POLE* mutations in cohorts studied in COSMIC and those in study by Buttura et al., which included 486 and 787 gastric cases, respectively, was low [3][28]. Therefore, further studies are needed to thoroughly evaluate the *POLE* mutational status in gastric cancer patients.

Mutational Status of *ARID1A* and MSI Phenotype

The most unfavourable outcome in patients treated with ICIs is rapid tumour growth (hyperprogressive disease, HPD), which can occur in 10% of gastric cancer patients [34]. A recent large study indicated that *ARID1A* mutational status could be predictive biomarker for indication of favourable response to 5-FU chemotherapy combined with PD-1 inhibitors in patients with high tumour mutational burden and MSI status [37]. ARID1A is a tumour suppressor, involved in transcription by remodelling chromatin in an ATP-dependent manner and was mutated in approximately 25% gastric cancer patients. Nonfunctional ARID1A was associated with the deficiency in DNA damage response, base excision repair (BER), nucleotide excision repair (NER), MMR, HRR, overexpression of cell cycle genes and PD-L1 pathway genes, *POLE* mutations, and overrepresentation of immune cell subtypes in the tumour microenvironment [37]. Most substitutions in *ARID1A* are C > T, which are also characteristic for MMR-deficient mutational signatures SBS6, SBS15, SBS20, and SBS44, together with HRR-associated SBS3 and BER-associated SBS30 [3]. Furthermore, analysis of immune-signature revealed that tumour environments of ARID1A-deficient tumours were infiltrated with specific subtypes of immune cells, such as subsets of CD4+, CD8+ T cells and NK cells, type 17 T-helper cells (Th17), and so on. Abundant Th17 infiltration was positively associated with better overall survival and chemosensitivity [37]. The authors also established that treatment with PD-L1 inhibitors could upregulate the Th17 population in tumours, which could serve as a priming therapy for establishing chemotherapy susceptibility. This strategy, if proved to be effective in further studies, could be beneficial for MSI-inoperable tumours. In addition, since AIRD1A-mutated tumours exhibited high MSI and tumour mutation burden, the authors speculated that targeted therapy against components of DNA damage response, such as ATR or

PARP, could be used in line with ICIs. It should be noted that other studies have also investigated the immune cell subsets, and particularly in the context of CD4+ and CD8+ T cells and PD-L1 expression status, there were conflicting results [38][39].

Research and clinical trials have shown that there is an unmet need for additional reliable biomarker(s) for the selection of gastric cancer patients who would benefit from ICIs. Currently, three FDA-approved biomarkers, indicative for ICIs treatment in cancers, are PD-L1 positivity by immunohistochemistry, MSI status, and tumour mutational burden, although the efficacy of the latter two has been challenged in several studies, as mentioned above.

4.3. Double Strand Break Repair by Nonhomologous End Joining

ID6 and ID8 were associated with defects in NHEJ, a mechanism responsible for the repair of double-strand breaks (DSBs) [2]. NHEJ directly joins two broken DNA strands by a template-independent mechanism and is active throughout the cell cycle, whereas HRR, which also repairs DSBs through a homology-dependent mechanism, is only active during the S and G2 phases [82]. DSBs are common in physiological cellular processes such as meiosis, class switch recombination, and V(D)J recombination [83]. Exogenous damaging factors, such as ionising radiation, ROS, and certain chemical compounds are also a source of DSBs. Misrepaired DSBs lead to chromosomal translocations and aberrations causing CIN, which may result in oncogenic transformation or cell death [84]. CIN is a hallmark in 49.8% gastric cancer cases, according to the TCGA study [35]. In addition to NHEJ, several other factors, such as impaired chromosome cohesion, spindle assembly, kinetochore–microtubule attachment and cell-cycle regulation contribute to CIN [85]. Nevertheless, defects and overexpression of key NHEJ proteins such as KUs, DNA-PKcs, DNA ligase IV, and XRCC4 have been reported in many cancers, including gastric cancer [40]. More importantly, defective, hyperactivated, or underactivated DNA repair could significantly affect treatment response, particularly resistance to therapy and survival outcomes, as NHEJ has a central role in radio- and chemotherapy resistance through hyperactivation of the involved proteins. Patients who showed therapy resistance or relapse and displayed overactivated NHEJ might benefit from NHEJ inhibitors. Several such inhibitors are being studied and are reviewed in a publication by Sishc and Davis [86]. For example, wortmannin, a DNA-PKcs and PI3K inhibitor, has radio-sensitising effects and was also shown to intensify the ionisation radiation effect in cancer cells [41]. LY294002, a quercetin derivative, has similar properties; however, in some studies it showed significant off-target activity [42]. NU7026 appears to be a promising compound due to its selectivity against DNA-PKcs and potency and the ability to enhance the effect of IR and etoposide [43]. Several DNA ligase IV inhibitors have also been studied, with SCR7 being the most potent one [41]. The clinical efficacy of NHEJ inhibition is under debate as this repair pathway prevents the genomic instability in normal cells through the repair of DSBs; however, NHEJ also drives carcinogenesis in cancerous or perhaps precancerous cells due to mutation accumulation in key protein members or due to the impairment of other DSBs repair pathways. Therefore, targeted cell delivery of NHEJ inhibitors should be considered in the future.

5. Reactive Oxygen Species

SBS18 is associated with damage caused by ROS [2][44]. Exo- or endogenously induced ROS generate nucleotide base damage which, if not repaired properly, can result in mutation. These include pollutants, radiation, smoking, drugs, xenobiotics, and food components. In relation to gastric cancer, a considerate amount of ROS is formed during *H. pylori* infection, mainly by neutrophils to kill the bacteria [87]. Endogenous sources of ROS are metabolic pathways in cellular organelles with high oxygen consumption, such as mitochondria, peroxisomes, and endoplasmic reticulum.

One of the most common ROS-induced base modifications, 8-Oxoguanine (8-oxoG), can mispair with adenine during DNA replication, causing G:C > T:A transversion mutations. It has been estimated that approximately 2400 of 8-oxoG sites per cell can be found in cells without additional exposure to exogeneous carcinogens [88]. OGG1 and MUTYH enzymes are DNA glycosylases that remove 8-oxoG from 8-oxoG:C pairs and the mispaired adenine from the daughter strand, respectively [89]. Germline biallelic *MUTYH* mutations can result in *MUTYH*-associated colorectal polyposis and predisposition to colorectal cancer [90]. Carriers of bi- and monoallelic *MUTYH* mutations are also at higher risk for the development of gastric polyps and gastric cancer [44][47][48][49]. WES of *MUTYH*-associated polyposis in colorectal cancer revealed a distinct mutational pattern, SBS36 with frequent 8-oxoG:A mismatches in cancer driver genes (*APC*, *KRAS*, *PIK3CA*, *FAT4*, *TP53*, *FAT1*, *AMER1*, *KDM6A*, *SMAD4*, *SMAD2*) [91]. Although signature SBS36 was not identified in gastric cancer samples in a study published by Alexander et al. in 2020, signature SBS18, present in gastric cancer samples, has a similar profile (Pearson correlation coefficient of 0.77) and possibly indicates a similar underlying mechanism, *MUTYH* mutations and defective base excision repair, which needs further validation [2][91]. In nonsporadic colorectal cancer, defective *MUTYH* results in a relatively modest mutator phenotype; nevertheless, it is an important risk factor for colorectal cancer [92].

Mutations in *MUTYH*-associated polyposis may result in excessive neoepitopes, which are able to trigger an immune response. One such case report has been published, investigating a colorectal cancer patient, who carried two inactive *MUTYH* alleles and did not respond well to chemotherapy. However, this patient responded to the administration of PD-1 inhibitor (nivolumab), which resulted in the reduction in tumour size and metabolic activity [45]. Mouw et al. also suggested that tumours, driven by *MUTYH* mutations, might be responsive to PD-1/PD-L1 inhibitors [93]. MUTYH also plays a role in the activation and phosphorylation of CHEK1 [94]. This tumour suppressor is involved in the homologous recombination repair pathway [95]. Deleterious mutations in *CHEK1* have been associated with responsiveness to PARP-inhibitor olaparib and longer progression-free survival, together with overall survival and a longer period free from pain progression [46]. Therefore, patients with sporadic gastric cancer with SBS18 could be further evaluated for *MUTYH* mutational status or base excision and homologous repair deficiency to assess responsiveness to targeted therapies with inhibitors. It could also be worth considering including SBS18 status in surveillance programs for high-risk patients (who carry *MUTYH* mutations). It is noteworthy to mention that there is an increased risk in the development of stomach polyps and stomach cancer in individuals with hereditary MUTYH-associated polyposis [96], who predominantly develop colorectal polyps and colorectal cancer; therefore, SBS18 signature of stomach epithelia could indicate malignant changes in stomach.

6. Helicobacter Pylori Infection

Individuals infected with *H. pylori* have significantly increased risk for gastric cancer in comparison with noninfected individuals [97]. *H. pylori* causes chronic gastric epithelial inflammation, which leads to tissue remodelling and neoplasm formation. CagA and VacA bacterial cytotoxins trigger the production of inflammatory cytokines in cells [98]. Sustained expression of CagA in gastric epithelial cells resulted in SBS3 and ID6 mutational signatures, which have been previously associated with BRCAness [50]. Interestingly, they were found in intestinal gastric cancer samples, despite the lack of *BRCA1/2* mutations [2][20]. These results suggested that CagA provokes transient BRCAness in host cells, thus causing genome instability [99]. So even after eradication of *H. pylori* in a patient, malignant transformation continues [100]. PARP inhibitors are not an option for the treatment of these tumours characterised by BRCAness, since the activity of BRCA1 is fully restored [101][102]. Additionally, whole exome sequencing of gastric cancer tissues from five individuals infected with *H. pylori* revealed enrichment in C:G > T:A transition variants, which were notably more prevalent in MSI tumours [103]. Analysis of the sequence context (GpCpNp; N any base) revealed that AID deaminase activity could presumably be involved in this mutational pattern. Additionally, this signature was also present in adjacent infected normal tissue. AID activity is strongly correlated with gastrointestinal chronic infections and tumourigenesis [51]. More experiments on infected gastric cell lines and animal models are necessary to study mutational signatures related to *H. pylori* infection. Perhaps such mutational signatures would prove useful as an early onset signature for screening and surveillance of patients at high risk for gastric cancer.

7. Mutational Signatures of Unknown Origin

The underlying mechanisms causing around half of the catalogued mutational signatures remain unknown. In gastric cancer, these are currently the following: SBS5, SBS40, SBS17a and SBS17b, SBS28, DBS4, ID5, and ID14 [2]. SBS5, SBS40, and ID5 appear to be more or less present in all cancer types. SBS5 has previously been attributed to a continuous mutational process in normal tissues, similar to SBS1, which has been ascribed to aging [6]. SBS5 origin is not well understood, but it was proposed to be associated with continuous exposure to ubiquitous metabolic mutagen as it was more prominent in kidney cancers originating from metabolite-absorbing kidney proximal tubular epithelium in comparison to those originating from cells of the cortical-collecting duct [6][104]. However, it was also identified in cell clones when analysing mutational signatures in cancer cell lines, and it continued to exist in daughter cells, even when no exogenous mutagen was present, implying that an unknown endogenous mechanism could be responsible for this phenomenon [14]. Notably, it is increased in bladder cancer samples with mutations in *ERCC2*, a base excision repair protein. Several *ERCC2* variants have been correlated to gastric cancer risk, and *ERCC2* expression levels may serve as a marker for chemoresistance in colorectal cancer [105][106][107]. Nevertheless, there have been implications that SBS5 may be contaminated with SBS16 with unknown origin [3], so further refinements are necessary to confirm the exact aetiology of SBS5 and to evaluate its potential relation to ERCC2 in gastric cancer. DBS4 and ID5 (and SBS40 in certain cancer types) also display a clocklike feature and are correlated to age at cancer diagnosis, implying they may be endogenously generated signatures.

Significant correlation was reported between the rate of somatic retrotransposition and SBS17a/b, suggesting a potential association between these signatures and APOBEC activity [14]. Interestingly, these signatures were present in stock cell lines but did not continue to be acquired in vitro even though the parent cells were overwhelmed with these signatures, arguing that a certain exogenous factor could be responsible for the underlying mechanism. SBS28 appears to be found in a limited group of cancer types and is associated with SBS10a and SBS10b, which are likely related to polymerase epsilon exonuclease domain mutations (*POLE*). Interestingly, SBS28 contributes to very high numbers of mutations when found in samples with SBS10a/b, even though the mutation numbers are much lower in samples lacking SBS10a/b [3]. It is worth mentioning that ID14, in addition to gastric cancer, was found only in colorectal and oesophagus cancer, which may point to a molecular mechanism common to all three types of cancer [2]. This signature characteristically generates large numbers of indels with no apparent evidence of defective MMR [3].

8. Conclusion

In the future, it will be important to understand signature penetrance and integrate genomic, epigenomic, transcriptomic and molecular markers for a more accurate cancer subtyping with defined hallmarks. These integrated signature profiles could offer predictive diagnostic and prognostic values in order to develop necessary frameworks to design successful patient-tailored treatment strategies. Understanding the genomic background of gastric cancer would together with molecular and clinical data help with patient stratification and selection of the most appropriate targeted therapy.

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