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Clinical importance of DNA repair in sporadic colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is the third major cause of cancer-related deaths worldwide. However, despite the scientific efforts to provide a molecular classification to improve CRC clinical practice management, prognosis and therapeutic decision are still strongly dependent on the TNM staging system. Mismatch repair system deficiencies can occur in many organs, but it is mainly a hallmark of CRC influencing clinical outcomes and response to therapy. This review will discuss the effect of the modulation of other DNA repair pathways (direct, excision and double strand break repairs) in the clinical and pathological aspects of colorectal cancer and its potential as prognostic and predictive biomarkers.

1. Introduction

Colorectal cancer (CRC) is the third major cause of cancer-related deaths worldwide. Every year, almost 1,000,000 new cases of CRC are diagnosed and 700,000 deaths from CRC are registered (Frederiksen et al., 2010; Siegel et al., 2017). The overall survival rate of patients with CRC is highly dependent on the disease stage at the time of diagnosis (Siegel et al., 2017). CRC is a multifactorial disease which occurs due to sequential and cumulative genetics and epigenetic alterations, including tumor suppressors, cell cycle regulators' genes and DNA mismatch repair (MMR) pathway in the colon mucosa cells (Migliore et al., 2011). It is well accepted that the molecular progression of CRC follows the classical model of adenoma-carcinoma sequence or vogelgram (Fearon and Vogelstein, 1990; Vogelstein et al., 1988). However, there is a growing body of evidences implicating other cellular and molecular alterations and their impact in CRC development and levels of aggressiveness.

Early CRC detection is still the most effective approach against this disease (NCCN, 2017). CRC staging basically relies on the use of tumor-node-metastasis (TNM) system and does not analyze any molecular aspects of the tumor as a routine (Galon, 2006; Kawakami et al., 2015). The current TNM staging system is inadequate and obsolete to be considered the only tool for therapeutic decisions, CRC recurrence and survival prediction after resection for stage II and III patients. It results in insufficient treatment of stage II CRC with 25% of disease recurrence, fast progression with metastasis and resistance to chemotherapy (Biagi et al., 2011; O'Connell et al., 2008) and excessive treatment of stage III CRC patients with 50% of disease recurrence (Bramsen et al., 2017; Tsikitis et al., 2014). Thus, biomarkers are indispensable for TNM refinement and accuracy, but due to tumor heterogeneity, it is still a challenge to find a unique molecular classification system with prognostic and predictive value.

Currently, to refine TNM prognostic accuracy, carcinoembryonic antigen (CEA) is recommended as a biomarker to detect the presence of metastasis and to follow up CRC patients. However, the use of CEA in early CRC diagnosis or recurrence still presents major limitations in terms of sensitivity (from 41% to 97%) and specificity (from 52% to 100%) (Dbouk et al., 2007; Duffy, 2001; Nicholson et al., 2015). So far, the combined use of TNM and CEA for the identification of patients who are at risk of developing distant metastases has not been recognized as being effective (Donizetti Silva et al., 2013).

As CRC has been defined as a complex and a heterogeneous disease, especially regarding outcomes and drug responsiveness, it is not surprising that it can be classified into various gene expression–based subtypes, which are also categorized by their specific molecular (including microsatellite instability (MSI) or chromosomal instability (CIN) and pathological profiles in colorectal molecular subtypes (CMS) (Guinney et al., 2015; Muller et al., 2016). Subtype CMS1 and CMS4 have worse prognosis (Guinney et al., 2015).

Mismatch repair system deficiencies can occur in many organs, but it is mainly a hallmark of hereditary CRC. Around only 15% of sporadic CRC present MSI as a direct consequence of defective MMR (dMMR)

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(mainly due to epigenetic silencing of MLH1, MSH2, PMS1 and/or PMS2 promoters), which is associated with a better overall survival rate and response to 5-fluoracil (5-FU)-based therapies (Sinicrope et al., 2011). In this context, the classical relevance of DNA repair system in sporadic CRC as a prognostic and predictive tool relies on the investigation of MSI presence in the tumor specimens. Therefore, considering this and the extensive participation of DNA repair modulation in virtually all the types of cancer, over the last decade other DNA repair pathways have been studied in the light of its predictive and prognostic values for colorectal cancer. Here we review the studies comprising the associations between gene and protein expression of the main components of direct, excision (base and nucleotide) and double strand break repair pathways and clinicopathological features, response to chemotherapy and survival in CRC.

2. Biological importance of DNA repair mechanisms in CRC

It is estimated that human cells suffer over 2×10^4 DNA damaging events every day, which are normally repaired by specific DNA repair pathways that assure the genomic integrity (Lindahl and Wood, 1999). The components of DNA repair system can be didactically classified into direct (which requires one protein/enzyme that act in one single step) and indirect repair (which requires several proteins/enzymes that act in several steps, including lesion recognition and strand excision, polymerization and ligation). Direct repair (DR) repairs DNA methylations; Base excision repair (BER) pathway is responsible for repairing oxidized bases and single-strand breaks (SSBs); Nucleotide excision repair (NER) pathway corrects pyrimidine dimers and bulky helix disorders; DNA double strand breaks (DSBs) are processed by homologous recombination (HR) and-homologous end joining (NHEJ) pathways.

Defective DNA repair is a common hallmark of cancer. DNA repair genes are frequently mutated in cancer, yet limited studies have proven their indispensable role in the disease prognosis and response to chemo- and radiotherapy. Hence, the biological significance of DNA repair mechanisms is supported by the fact that the deregulation of such system may contribute both to the initiation and progression of cancer. In addition, by repairing the damage caused by chemo- and radiotherapy to the DNA molecule of the cancer cell, the DNA repair systems may implicate in resistance to treatments. Therefore, the efficacy of cancer treatments - which rely on structural and metabolic dysfunction of DNA to induce the death of neoplastic cells – may be severely compromised, culminating in poor clinical outcomes. Consequently, there is still a search for new therapeutic approaches based on the principle of using internal deficiencies in DNA repair mechanisms, in favor of increasing the cellular sensitivity to agents that cause this sort of lesions. Thus, the ability of neoplastic cells or even neoplastic stem cells to recognize and initiate DNA repair is possibly the key mechanism for overcoming the therapeutic resistance and recurrence of cancer (Torgovnick and Schumacher, 2015).

In CRC, the classic relevance of DNA repair pathways can be attributed to the mismatch repair pathway, since germline deleterious mutations in this pathway genes are responsible for the hereditary version of colorectal neoplasms occurrence and confer a 70% lifetime risk of CRC development and an increased risk of developing other cancers (Sehgal et al., 2014). However, in sporadic CRC, the MMR deficiency results from the loss of expression of at least one out of four of its main components, mainly MLH1 and/or MSH2 by epigenetic mechanisms and leads to MSI in 15% of the cases (Sargent et al., 2010). In addition, also considering the context of DNA repair and damage, the gastrointestinal tract is a main target for oxidizing elements, which are highly mutagenic (Aran et al., 2016; Obtułowicz et al., 2010). These factors are responsible for increasing the susceptibility of colonic epithelium to mutations due to base oxidation, mispairings and strand breaks, which can lead to loss of genomic integrity and colorectal carcinogenesis. Since MMR system is involved in post-replicative damage recognition and signaling, inactivity of this pathway may be one suitable explanation for the process of malign transformation preferably affecting proliferating cells, such as colon epithelial tissues (Fearon, 2011).

However, the relationship between DNA damage and its repair is far more complex than its own concept, since no single pathway can repair all types of injury efficiently. Some lesions are substrate for more than one pathway, and there is evidence of interaction between proteins involved in distinct pathways (Nagel et al., 2014). This interaction is probably responsible for generating different degrees of malignancy and modulating the carcinogenic process as well as the response to therapeutic agents in CRC (Bardhan and Liu, 2013).

3. Mismatch repair: MMR status has promising prognostic and predictive value in CRC patients

MMR is one of DNA repair pathways that aims to maintain genomic stability when DNA replication and recombination errors occurs (Iyer et al., 2006). This pathway recognizes and repairs erroneous insertions, deletions and misincorporation of bases, but also repairs mispairs due to endogenous (oxidative reactions) and exogenous (chemicals and physical agents) kinds of DNA damage (Li, 2008). Study of the biochemistry of the MMR proteins has revealed that recognition of mismatches and insertion/deletion loops is performed by a heterodimers of either *MSH2* and *MSH6* or *MSH2* and *MSH3* (Hsieh and Kazuhiko, 2009). While the MLH1, PMS2, and PMS1 proteins act primarily by repairing the base-base mismatches and insertion/deletion loops, the heterodimer of MLH1-PMS2 proteins executes the repair of the mismatches in conjunction with other molecules (Kheirelseid et al., 2013).

MMR is the most studied DNA repair pathway in the context of CRC pathological and clinical features, and deficiencies in this pathway result in tumors with MSI. Microsatellites are defined as repeated DNA sequences that consists in 2–5 base pairs, usually occurring 10–60 times and are scattered throughout coding and noncoding regions of the genome, compounding 3% of the genome (Bupathi and Wu, 2016).

It is well established that two distinct types of CRC - according to the MMR status - exist: MMR-proficient (pMMR) and MMR-deficient (dMMR). A germline mutation in one of the main MMR components (most frequently MLH1 or MSH2 and rarely MSH6 and PMS2), is the source of MMR deficiency in patients with Lynch syndrome (LS), previously referred as hereditary non-polyposis colorectal cancer (HNPCC), which comprises 0.8–5% of all CRC cases (Boland, 2005; Kawakami et al., 2015; Lynch, 1966; Mecklin, 1987). dMMR is also observed in 10–20% of patients with sporadic CRC, usually caused by *MLH1* promoter hypermethylation and consequent loss of protein expression (Hewish et al., 2010). Immunohistochemistry (IHC) in colorectal tumors for MLH1 and MSH2 is a rapid, sensitive and highly specific method for screening for MMR defects (Overbeek et al., 2008). Search for dMMR can be performed by IHC by testing at least one of the four main MMR proteins (MLH1, MSH2, PMS2, and MSH6) or by directly searching MSI in DNA-based test for unclear sporadic CRC or hereditary CRC confirmation (Funkhouser et al., 2012; Sepulveda et al., 2017).

dMMR CRC shows several distinct clinicopathological features and may have some influence in response to chemotherapy and serve as a predictive factor to 5-FU response in CRC patients. dMMR/MSI is considered a prognostic factor for unfavorable outcomes, which are represented by predominant occurrence in proximal colon, lymphocytic infiltrate, poorly differentiated tumor cells and presence of mucin or signet ring appearance. Conversely, dMMR in CRC tumors favors response to 5-FU–based chemotherapy in comparison to patients with pMMR CRC receiving the same scheme (Koopman et al., 2009; Miyakura et al., 2001; Ryan et al., 2017; Sepulveda et al., 2017).

In selected stage II and stage III CRC the fluoropyrimide (5-FU or capecitabine)-based adjuvant chemotherapy is considered the first line of care (André et al., 2009, 2004; Zhang et al., 2016b; Ryan et al., 2017) and is commonly used with other chemotherapeutic agents, such as

irinotecan, leucovorin (LV) and oxaplatin (Zhang et al., 2016b). Despite the amount of reports, current clinical data about 5-FU-based adjuvant chemotherapy in patients with dMMR is still considered conflicting, mainly due to bimodal age distribution of CRC patients, limited sample size, inclusion of multiple tumor stages and heterogeneous 5-FU-based adjuvant regimens (Kawakami et al., 2015; Zhang et al., 2016b; Ryan et al., 2017). Some studies considered that 5-FU-based adjuvant chemotherapy was ineffective in stage II and III CRC patients with dMMR tumors, since it does not improve overall and disease-free survival (Ribic, 2003; Sargent et al., 2010; Hutchins et al., 2011; Webber et al., 2015). In counterpart, other studies have shown that dMMR CRCs had a similar or even greater benefit from 5-FU-based adjuvant treatment, when compared to pMMR CRCs, with better overall and disease-free survival rates (Elsaleh et al., 2000; Hemminki et al., 2000; Kim et al., 2007; Westra et al., 2005; Popat et al., 2005; Guastadisegni et al., 2010).

In stage II dMMR CRC patients treated with surgery plus 5-FU or surgery alone, the last ones presented better overall survival (Ribic, 2003), which may indicate that these patients do not benefit from adjuvant 5-FU-based therapies (Kawakami et al., 2015). Conversely, stage III dMMR CRC patients submitted to the same regimens, dMMR disfavored disease recurrence and delayed time to response (TTR), but improved survival rates when compared to pMMR tumors. However, all stage III patients received adjuvant chemotherapy independently of MMR status (Des Guetz et al., 2009a; Kawakami et al., 2015; Webber et al., 2015). Despite still contradictory, these findings strengthen the possibility of including MMR status as a predictive biomarker for 5-FU based therapy (Ryan et al., 2017).

The addition of other chemotherapy agents to 5-FU (e.g., FOLFOX and FOLFIRI) efficiently improves disease-free survival (DFS) and overall survival (OS) in comparison to 5-FU with leucovorin isolated in stage III dMMR CRC patients to FOLFOX regimen (André et al., 2009; Devaud and Gallinger, 2013; Gavin et al., 2012; Zaanan et al., 2009, André et al., 2015). A meta-analysis of treated and untreated state II/III with high-MSI (MSI-H) colorectal tumors showed that MSI-H status, in addition to predicting better prognosis, also is a predictive factor of non-response to chemotherapy (Des Guetz et al., 2009b). Alternatively, another meta-analysis in metastatic CRC patients (mCRC) found no benefit of chemotherapy in terms of response ratio for MSI-H patients compared with microsatellite stable (MSS) patients, showing that this phenotype does not predict chemotherapy response in this subset of patients (Des Guetz et al., 2009a). Regarding targeted therapy, it seems that bevacizumab - monoclonal antibody of Vascular Endothelial Growth Factor (VEGF) - in combination with FOLFOX has a potential benefit in stage II/III dMMR CRC patients' survival (Pogue-Geile et al., 2013). It may be since dMMR CRC patients also present higher serum VEGF levels, given the well-defined target of this antibody or anti-angiogenic treatment in general (Hansen et al., 2011). Also, studies revealed that patients with advanced CRC who possess a *BRAF* mutation have significantly poorer outcomes as measured by PFS and OS and have a decreased response rate to anti-EGFR therapy relative to those with non-mutated *BRAF*(Sepulveda et al., 2017)."

Immunotherapy-based treatment is approved for use in metastatic/refractory dMMR CRC patients by the Food and Drug Administration (FDA) in the United States due to the strong T cell response induced by large amounts of neoantigens (Kelderman et al., 2015) related to the specific antigen-driven immune responses caused by dMMR (Phipps et al., 2015). dMMR CRC have a highly up-regulated expression of multiple immune checkpoint proteins, including Programmed Death-ligand 1 (PD-L1). This characteristic is not exclusive of tumor cells, but it also occurs in tumor-infiltrating lymphocytes and/or myeloid cells (Llosa et al., 2015; Ryan et al., 2017; Taube et al., 2014) and the mechanism of immune-based therapy involves the blockade of these immunoregulatory system (Ryan et al., 2017). The first phase I trial evaluated nivolumab in CRC and only one patient presented complete response out of 20 treated (Brahmer et al., 2010). A study phase II showed compared clinical response of pembrolizumab monotherapy in patients with previously treated, progressive metastatic tumors, with or without dMMR, and it was demonstrated that dMMR CRC had both better progression free survival (PFS) and OS (Le et al., 2015). The European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) is now recommending MSI testing as a result of its immune check-point inhibitors treatment strong predictive value in patients with mCRC (Van Cutsem et al., 2016; NCCN, 2017). dMMR occurs in less than 5% of mCRC (Funkhouser et al., 2012) and immune checkpoint blockade treatment in advanced CRC patients with pMMR disease has been associated with unsatisfactory responses (Myint and Goel, 2017). However, there are studies recruiting patients with advanced unresectable or metastatic CRC aiming to define MMR status as predictive biomarker for immunotherapy-based treatment (Clinical Trials Identifier: NCT02981524; NCT03396926; NCT02563002; NCT02460198)

In sum, most sporadic CRC is pMMR, which is associated with worse survival in comparison to dMMR. Patients with resected stage II dMMR CRC have good prognosis, but the lack of evidence on 5-FU-based chemotherapy benefit supports the use of other chemotherapy schemes. For stage III CRC patients, MMR status does not influence chemotherapy decisions, but it seems that dMMR is an indicative of good prognosis and a predictive factor of non-response, although literature data on this topic are still conflicting (Ryan et al., 2017). Finally, the ESMO and NCCN recommended MSI testing due to its strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC which aim to use immunotherapy-based treatment, but there are many studies recruiting patients to define the real predictive role of MMR status in CCR patients treated with immunotherapy.

4. Direct repair: *MGMT* methylation status is a potential predictive biomarker of response to treatment to temozolomide (TMZ) in mCRC

O^6-Methylguanine (O^6-MG)-DNA-methyltransferase gene (*MGMT*) encodes the DNA-repair protein O^6-alkylguanine (O^6-AG) DNA alkyltransferase (AGT), which removes alkyl groups from O^6 position of guanine to protect normal cells from exogenous carcinogens (D'Incalci et al., 1988; Pegg, 1990). This protein is unique among DNA repair proteins since it acts by itself to eliminate DNA adducts. The AGT protein is a DNA repair enzyme that is normally expressed in all normal human cells and protects DNA from damage caused by alkylating agents (Gerson, 2004).

MGMT is located on chromosome 10 at 10q26 and encodes five exons and four introns. The 5′ promoter region contain several transcription factors recognition sequences and has many GC base pair repeats (CpG islands), which are very common methylation sites (Natarajan et al., 1992). Loss of MGMT expression, often through MGMT promoter methylation, is clinically relevant, and was first reported in 1999 (Esteller et al., 1999). While the overexpression of MGMT is known for its influence in reducing the risk of carcinogenesis and the risk of mutations after exposure to alkylating agents, such as TMZ (Amatu et al., 2016), loss of MGMT results in enhanced cytotoxicity of classic alkylators, such as cyclophosphamide, but also of topoisomerase I inhibitors and irinotecan (Friedman et al., 1995, 2002; Khan et al., 2008).

It is well known that colorectal mucosa is constantly exposed to exogenous carcinogens. Consequently, it is fundamental to preserve a competent DNA repairing system to protect normal cells from mutagenesis. MGMT restores mutagenic O^6-methylguanine to guanine in normal colonic tissue, preventing DNA alkylation damage (Farzanehfar et al., 2013). The relevance of *MGMT* in CRC carcinogenesis is widely accepted, and reduced MGMT expression has been documented in tumor in comparison to normal colon tissues (Kuan et al., 2015). MGMT gene promoter methylation also plays an important role in colorectal

carcinogenesis, occurring in about 30–40% of all CRC cases (Esteller et al., 2001; Shen et al., 2005). Indeed, *MGMT* promoter methylation is a useful marker to identify early stages of CRC (Shen et al., 2005).

Low frequency of *MGMT* methylation has been detected in normal colorectal mucosa taken from the margin of the resected CRC as well as in individuals without CRC (Ahlquist et al., 2008; Nagasaka et al., 2008). Thus, it has been accepted that the modulation of *MGMT* expression through methylation seems to be more involved with colorectal carcinogenesis than with the prognostic aspects of the disease, since it also occurs in healthy intestinal tissue. It may suggest that *MGMT* gene silencing is only one of several steps required to accumulate DNA damage and to lead cells to malignancy. Loss of *MGMT* has therefore been defined as a *field defect*, i.e., it is not completely necessary nor sufficient for the progression of cancer, but it represents one of several steps involved with the carcinogenesis (Nagasaka et al., 2008).

MGMT loss also plays a role in MSS CRC through a mechanism of chromosomal instability (Shen et al., 2005), but it is more frequent in this MSI CRC phenotype, suggesting that *MGMT* promoter methylation selects dMMR clones (Svrcek et al., 2010). In fact, a second level of defense against DNA damage is represented by MMR pathway, which leads the cell to apoptosis in the presence of serious genomic changes (Allan and Travis, 2005).

4.1. Prognostic value of MGMT promoter methylation or loss of expression

Relevant literature has been registering the scientific efforts to discover the diagnostic, prognostic and predictive relevance of MGMT in colorectal cancer (Farzanehfar et al., 2013; Ju et al., 2011; Kim et al., 2010; Krtolica et al., 2007; Leguisamo et al., 2017; Nagasaka et al., 2008; Nilsson et al., 2013; Shima et al., 2011; Sinha et al., 2013). The first study to correlate *MGMT* promoter methylation and prognostic features of tumor aggressiveness showed no association with clinicopathological characteristics and no influence in overall survival (Krtolica et al., 2007). Later, two other studies presented conflicting data regarding the association of CRC clinical features and loss of MGMT expression in tumor tissues (Ju et al., 2011; Nagasaka et al., 2008). As summarized in Table 1, MGMT promoter methylation or loss of protein expression was associated with distal tumor location (Shima et al., 2011), late tumor stage (Ju et al., 2011; Nilsson et al., 2013; Sinha et al., 2013), high grade tumors (Leguisamo et al., 2017; Oliver et al., 2014) and tubular adenocarcinoma (Zhang et al., 2016a)– all features of tumor aggressiveness. A meta-analysis of 28 studies attempted to demonstrate evidence that MGMT may be a candidate for a tumor suppressor in CRC by testing its prognostic value. Unfortunately, the results were inconclusive in relation to clinicopathological data due to the heterogeneity of studies included. Even so, this meta-analysis also discussed the importance of MGMT as a potential drug target of CRC (Zheng et al., 2015). Nevertheless, usually, there are many inconsistent results for associations with clinical and pathological factors, possibly due to the experimental designs of the studies, low statistical power or erroneous investigation of the methylated regions.

Currently, there is no evidence in literature that MGMT can be utilized as prognostic biomarker. Six studies have attempted to demonstrate the role of MGMT, one author described that MGMT methylation may play a protective role (Nilsson et al., 2013) another study showed that high expression of MGMT has a better outcome (Oliver et al., 2014). Nevertheless, four studies did not show correlation of low expression or methylation of MGMT with overall survival (Krtolica et al., 2007; De Maglio et al., 2015; Shima et al., 2011; Zhang et al., 2015a) or progression-free survival (Oliver et al., 2014).

4.2. MGMT promoter methylation or loss of expression predictive value

MGMT is an ascertained predictive biomarker in melanoma and glioblastoma, where alkylating agents are the first line treatment (Tuominen et al., 2015; Walter et al., 2015). Particularly in glioma, loss of MGMT expression affects both tumor progression and response to chemotherapy (Esteller et al., 2001). Dacarbazine and temozolomide (TMZ) deliver a methyl group to adenine or guanine in DNA. The primary cytotoxic lesion, O^6-methylguanine (O^6-MeG) is normally processed by MGMT protein in a one-step methyl transfer reaction. Thus, MGMT inactivation may confer sensitivity to alkylating agents (Amatu et al., 2013; Esteller and Herman, 2004).

In case of loss of MGMT, these lesions can be tolerated by MMR pathway (Zhang et al., 2012), which is the main rational for the use of TMZ or dacarbazine in dMMR CRC with *MGMT* promoter methylation. However, the effectiveness of alkylating agents in the treatment of CRC is not clear (Clinical Trials Identifier: NCT02414009; NCT01781403; NCT01051596; Hochhauser et al., 2013). In the past, fluoropyrimidine-resistant patients who received dacarbazine with other drugs had response rates between 19%–33% (Içli et al., 1999). When TMZ is associated with other drugs in unselected metastatic CRC patients, it did not show improvement in the disease prognosis (Khan et al., 2008). Meanwhile, using the appropriate molecular rational, recent studies separate response rate in patients with mCRC exhibiting loss of MGMT expression. A case report described two patients with mCRC and loss of expression of MGMT who had an impressive clinical response and partial tumor regression with the use of TMZ as a single agent (Shacham-Shmueli et al., 2011). In addition, phase II studies with CRC patients with MGMT promoter methylation or loss of expression and treated with TMZ, are presenting objective response rates between 2,7–53% (Calegari et al., 2017; Hochhauser et al., 2013; Pietrantonio et al., 2014, 2015), with clinical significance in two studies (Pietrantonio et al., 2014, 2015), as summarized in Table 2.

Table 1
Studies reporting the prognostic value of MGMT promoter methylation or MGMT loss/low protein expression in CRC patients.

Author	n	Method	MGMT (% of cases)*	Clinicopathological feature association	*p*	Clinical outcome		*p*
Krtolica et al. (2007)	85	MSP	43.0	NA		OS (months)a	35.5 ± 6 vs. 23.1 ± 3.2	NS(1)
Nagasaka et al. (2008)	219	COBRA	36.1	Stage I and II	0.04(1)	NE		
Ju et al. (2011)	78	PS	26.9	Stage IV	0.043(1)	NE		
Kim et al. (2010)	285	PS	21.0	NA		NE		
Shima et al. (2011)	855	QMSP	38.0	NA		OS (HR)a	1.0 [CI 0.88–1.32]	NS(4)
		IHC	37.0	Distal CRC	0.014(1)	OS (HR)b	1.11 [CI 0.87–1.41]	NS(4)
Nilsson et al. (2013)	111	PS	34.0	Stage IV	< 0.0001(2)	OS (HR)a	0.36 [CI 0.15–0.87]	0.049(4)
Farzanehfar et al. (2013)	40	QMSP	27.5	NA		NE		
Sinha et al. (2013)	124	MSP	47.0	Stage III and IV	0.018(1)	NE		
Oliver et al., 2014	123	IHC	73.7	High grade tumors	0.011(3)	OS (HR)b	3.73 [CI 1.35–10.33]	0.011(4)
						PFS (HR)b	1.55 [CI 0.81–2.99]	NS(4)
De Maglio et al. (2015)	53	PS	64.2	NA		OS (days)a	163 vs. 193	NS(1)
Leguisamo et al. (2017)	70	qPCR	74.2	High grade tumors	0.027(3)	NE		
Zhang et al. (2016a,b)	385	IHC	24.2	Tubular adenocarcinoma	0.011(2)	OS (months)b	19.83 vs. 23.57	NS(1)

Table 2
Studies evaluating the predictive value of MGMT promoter methylation or MGMT loss/low protein expression in metastatic CRC.

Author	Method	ITT population	Treatment	Primary endpoint		*p*	Conclusion
Amatu et al. (2013)	MSP	68	Dacarbazine	ORR	3%	NS(1)	Primary endpoint not met
Hochhauser et al. (2013)	MSP	37	Temozolomide	ORR	2.7% [CI 0.1-14.2%]	NS(2)	Primary endpoint not met
Pietrantonio et al. (2014)	MSP	32	Temozolomide	ORR	12%	< 0.05(1)	Primary endpoint met in CRC harboring MGMT promoter methylation
Zhang et al. (2016a,b)	IHC/MSP	385	Oxaliplatin Irinotecan	PFS (months)*	7.0 vs. 9.17 7.17 vs. 7.07	0.08(3) 0.025(3)	Primary endpoint met in irinotecan treated CRC with low MGMT expression
Pietrantonio et al. (2015)	IHC	32	Temozolomide	ORR	53%	p < 0.0001(1)	Primary endpoint met in CRC harboring MGMT promoter methylation
Amatu et al. (2016)	MSP	29	Temozolomide	PFS rate at 12 weeks (%)	10.3% [CI 2.9-24.6%]	NA	Primary endpoint not met
Sartore-Bianchi et al. (2017)	MB/IHC	71	Temozolomide or dacabarzine	DCR	34.3%	0.001(2)	Primary endpoint met in CRC harboring MGMT promoter methylation and low MGMT protein expression
Calegari et al. (2017)	MSP	80	Temozolomide	ORR	10%	NS(1)	Primary endpoint not met

MSP: methylation-specific PCR; IHC: immunohistochemistry; MB: methyl-BEAMing; ITT: intention to treat; ORR: overall response rate (complete and partial response); PFS: progression-free survival; DCR: disease control rate (complete response + partial response + stable disease); *: low- vs high-MGMT expression; CI: confiance interval; (1): student t-tests or Fisher exact test; (2): regression; (3): log-rank; NS: no significance.

Furthermore, MGMT hypermethylation or low MGMT protein expression and use of dacarbazine or TMZ was associated with better disease control rate in patients with mCRC (Sartore-Bianchi et al., 2017) and with improvement in PFS when oxaliplatin or irinotecan are added (Zhang et al., 2016b).

4.3. MGMT conclusions

Despite the amount of evidence, predictive and prognostic role of *MGMT* promoter methylation or loss of expression is not yet defined in CRC. The clinicopathological data reveals many inconsistent results for associations with prognostic factors, possibly due to the experimental designs of the studies, low statistical power, erroneous investigation of the methylated regions or different methods to analyze MGMT expression. Nevertheless, testing *MGMT* methylation status or protein expression in colorectal tumor specimens has an interesting potential as a predictive biomarker, especially if the effectiveness of TMZ as a single agent or in combination with other drugs treatment in refractory mCRC is confirmed.

5. Base excision repair: a promising but still neglected pathway in CRC

Base excision repair (BER) is a multi-step repair pathway acting on damaged bases caused by alkylation, oxidation or deamination and proceeds through a sequence of reactions according to the initial base lesion (Rouleau et al., 2010). Shortly, BER complete activity involves the coordinate actions of DNA glycosylases, endonucleases, DNA polymerases and DNA ligases. BER is initiated upon base removal by one of several substrate-specific DNA glycosylases, such as *N*-methylpurine DNA glycosylase (MPG) and 8-oxo-guanine glycosylase (OGG1). Once the enzymatic BER steps are initiated, toxic intermediates such as apurinic/apyrimidinic (AP) sites and single strand breaks (SSB) are generated. Effective BER completion is coordinated by an important secondary element, the chromatin associated enzyme poly-(ADP-ribose) polymerase or PARP. PARP is activated upon binding to sites of SSB, allowing the recruitment of downstream BER enzymes and the conclusion of the repair procedure (Maynard et al., 2009).

BER pathway has a very significant role in CRC carcinogenesis. Colon epithelium is physiologically constantly renewed and is largely exposed to oxidative stress (Obtułowicz et al., 2010) caused by exposition to a variety of exogenous mutagens (cigarette smoking, alcohol, overcooked red meat, processed saturated fat, etc.) present inside the lumen of the bowel or in the blood (Potter, 1999); or by colon chronic inflammation, which affects cellular metabolism (Itzkowitz, 2004) and enhances epithelial cell turnover and favors neoplastic transformation (Slyskova et al., 2012).

The well-known BER relevance in CRC is related to the mutation in the *MUTYH* gene, which is responsible for a predisposing condition to CRC termed MUTYH associated polyposis (MAP) and is responsible for 0.3%–1% of all CRC (Nielsen et al., 2011). Patients carrying *MUTYH* mutations (Tyr165Cys or Gly382Asp) tend to develop multiple adenomatous colon polyps during their lifetime and have an increase of 28 to 93-fold risk of CRC (Farrington et al., 2005; Lubbe et al., 2009). MUTYH is a DNA glycosylase involved in oxidative DNA damage repair and repair of post-replicative mispairs within DNA replication (Zhang et al., 2015a). However, other BER components have been drawing attention in the context of sporadic CRC carcinogenesis, prognosis and response to chemotherapy in the last decade. Table 3 summarizes the main studies suggesting the changes in BER genes and proteins expression as prognostic and predictive biomarkers.

5.1. DNA glycosylases: OGG1 and MPG

The antioxidant potential in CRC tissues is impaired in comparison to healthy intestine tissue (Kondo et al., 2000; Park et al., 2001). Many observations suggest the role of oxidative stress in colon cancer pathogenesis. The most abundant oxidatively modified lesions in DNA is the promutagen 8-hydroxydeoxyguaninosine (8-oxodG) and it is the substrate for 8-oxoguanine DNA glycosylase (OGG1) (Saebø et al., 2006; Slyskova et al., 2012).

In the context of CRC prognosis, changes in *OGG1* gene expression were reported in normal colic tissues, colorectal adenocarcinomas and CRC patients' leukocytes. In normal colic tissue, *OGG1* gene expression was not associated with overall survival probability (Dziaman et al., 2014a). Regarding *OGG1* gene expression in CRC specimens, the results are conflicting so far. Low expression of *OGG1* in colorectal adenocarcinomas (in comparison to healthy surrounding tissues) was correlated to distal and advanced tumors (Santos et al., 2014) but also higher *OGG1* mRNA levels were shown to be associated with high grade tumors (Leguisamo et al., 2017).

Finally, higher levels of expression of *OGG1* were found in leukocytes of patients with malignant tumors in comparison to the healthy ones or the ones with adenomas. However, no prognostic value were associated (Obtułowicz et al., 2010).

MPG (also known as AAG or MDG) is a monofunctional DNA glycosylase and has a special role in BER pathway. Differently from OGG1, MPG addresses alkylation rather than oxidative stress (Whitaker et al., 2017). Augmented sensitivity to alkylating agents has been detected by modulating BER components in preclinical studies, which may signify

Table 3
BER components expression in CRC neoplasms as prognostic and predictive biomarkers: recent discoveries.

Pathway component	n	Product	Clinicopathological feature association	*p*	Clinical Outcome			*p*	Author
OGG1	low expression	49	mRNA	Distal tumors	< 0.05(1)	NE			Santos et al. (2014)
				Stage III and IV					
		40	mRNA	NE		OSP60 a	47%	NS(6)	Dziaman et al. (2014a,b)*
	high expression	70	mRNA	High grade tumors	0.042(2)	NE			Leguisamo et al. (2017)
MPG	high expression	70	mRNA	High grade tumors	0.031(2)	NE			Leguisamo et al. (2017)
				Lymphatic invasion	0.044(2)				
		72	protein	Right sided CRC	0.009(1,3)	PFSb	Shorter	0.004(5)	Azambuja et al.(2017)
				T3-T4	< 0.001(1,3)				
				Stage III and IV	< 0.001(1,3)				
				Lymphatic invasion	< 0.001(1,3)				
				Perineural invasion	0.011(1,3)				
				N+	< 0.001(1,3)				
APE1	low expression	49	mRNA	Distal tumors	< 0.05(1)	NE			Santos et al. (2014)
				Stage III and IV	< 0.05(1)				
	high expression	70	mRNA	Stage III and IV	0.018(2)	NE			Leguisamo et al. (2017)
PolB	high expression	97	mRNA	N+	< 0.05(1)	OSa	Worse	0.0219(5)	Iwatsuki et al. (2009)
				Lymphatic invasion	< 0.05(1)				
				Liver metastasis	< 0.05(1)				
				Distant metastasis	< 0.05(1)	RRa	1.270 [CI 0.82–2.06]	0.278(4)	
				Stage III and IV	< 0.05(1)				
		70	mRNA	N+	0.003(2)	NE			Leguisamo et al. (2017)
				Lymphatic invasion	0.024(2)				
				Perineural invasion	0.003(2)				
				Stage III and IV	0.001(2)				
		72	protein	Right sided CRC	0.03(1,3)	PFSb		NS(5)	Azambuja et al. (2017)
				T3-T4	< 0.001(1,3)				
				Stage III and IV	< 0.001(1,3)				
				Lymphatic invasion	0.04(1,3)				
				N+	0.01(1,3)				
Fen1	unchanged	72	protein	NA		PFS b		NS(5)	Azambuja et al. (2017)
PARP1	high expression	56	mRNA	Stage III and IV	0.028(4)	PFS (years) b	Shorter	< 0.012(5)	Alhadheq et al. (2016)
						OS (HR) b	3.083 [CI 1.944–8.24]	0.012(4)	
	low expression	70	mRNA	Lymphatic invasion	0.016(2)	NE			Leguisamo et al. (2017)
				Perineural invasion	0.043(2)				
		49	mRNA	Distal tumors	< 0.05(1)	NE			Santos et al. (2014)
				Stage III and IV	< 0.05(1)				
		52	protein	NA		OSP60 a	66%	NS(6)	Dziaman et al. (2014a,b)*
		151	protein	Dukes C	0.018(3)	NE			Sulzyc-Bielicka et al. (2012)
XRCC1	high expression	180	protein	NA		Early treatment failure (OR) b	1.376 [CI 0.625–3.028]	0.428(4)	Huang et al. (2013)
		49	mRNA	NA		NE			Santos et al. (2014)
		70	mRNA	High grade tumors	0.042 (2)	NE			Leguisamo et al. (2017)
		72	protein	Stage III and IV	0.001(1,3)	PFS b		NS(5)	Azambuja et al. (2017)
				Lymphatic invasion	0.001(1,3)				
				N+	< 0.001(1,3)				

NE: not evaluated; NA: no association; OS: overall survival; PFS: progression free survival; OSP: overall survival probability; RR: relative risk; HR: hazard ratio; OR: odds ratio; a: low vs. high expression; b: high vs. low; (1): chi-square test; (2): multiple linear regression analysis; (3): Fisher's exact test (two sided); (4): univariate/multivariate; (5): log-rank; (6): log-rank/univariate regression; NS: no significance; *normal colon tissue.

that changes in this pathway is a potential target for chemotherapy potentiation (Kinsella, 2009). Thus, the possible relevance of MPG in CRC is associated with TMZ-based treatment response, since the repair of TMZ-induced base damage starts with the recognition and removal of the damaged bases by MPG. Nevertheless, MPG role TMZ response to treatment in CRC was only assessed *in vitro* (Leguisamo et al., 2017).

Regarding MPG prognostic role, high expression of MPG was reported to be associated with several features of tumor aggressiveness, such as more aggressive histological subtypes, high grade tumors, presence of perineural and lymphatic invasion, right sided-CRC, late stages and shorter disease free survival (Azambuja et al., 2017; Leguisamo et al., 2017).

5.2. APE1

APE1 (human apurinic/apyrimidinic endonuclease 1) is the main BER AP endonuclease involved in DNA repair, transcriptional regulation and redox signaling (Ballista-Hernández et al., 2017). It has a 3′-phosphodiesterase activity and initiates repair of AP sites in DNA by hydrolyzing the phosphodiester 5′ backbone (Kelley and Parsons, 2001). APE1 protects cells against the toxic effects of endogenous and exogenous agents including chemotherapeutic agents (Fleck, 2004). CRC patients with reduced APE1 gene expression are more prone to present distal tumors (Santos et al., 2014). However, regarding TNM staging, the current literature offers two studies with contradictory results. While one study showed that low *APE1* gene expression is associated with the occurrence of more advanced tumors (Santos et al., 2014), the other study shows the contrary (Leguisamo et al., 2017).

5.3. Polβ

DNA Polymerase β (Polβ) is localized in chromosome 8 and is the main polymerase involved in BER. It has two catalytic activities, deoxyribose phosphate (dRP) lyase and polymerase activities. APE1 incises the AP site and leaves 3`-OH and 5`-dRP groups. POLβ removes the dRP group with its lyase activity and fills in the missing nucleotide (Lavrik et al., 1998). Polβ is essential in the DNA repair system mediated through BER machinery required for DNA maintenance, replication, recombination and drug resistance. In CRC clinical context, higher levels of Polβ gene and protein expression are associated with lymph node and distant metastasis, advanced TNM stages and right-sided tumors (Azambuja et al., 2017; Iwatsuki et al., 2009; Leguisamo et al., 2017). Furthermore, high Polβ protein expression is also correlated with worse prognosis (Iwatsuki et al., 2009).

5.4. PARP-1

Poly(ADP-Ribose) Polymerase-1 (PARP-1) is a nuclear enzyme, also part of the BER pathway, which is involved in cellular response to DNA damage and DNA metabolism, preserving genome integrity from DNA-strand breaks. This enzyme is also responsible for transcriptional regulation, telomere cohesion and mitotic spindle formation during cell division, intracellular trafficking and energy metabolism (Alshammari et al., 2014). The main clinical relevance of PARP in oncology relies on the use of PARP inhibitors (iPARP), following the synthetic lethality rational (Kaelin, 2005). Thus, testing PARP-1 expression in neoplastic tissues may be a useful molecular tool for patient individual chemo sensitivity, drug effectiveness and disease response to iPARP. Mechanistically, PARP-1 overexpression may occur in reason of oxidative stress and inflammation (Aguilar-Quesada et al., 2007; Storr et al., 2012), both crucial factors involved with CRC carcinogenesis.

In theory, targeting aberrant DNA repair colorectal tumors (e.g., dMMR/MSI-H) with iPARP could be a successful strategy. Six clinical trials to assess the effects of iPARP in CRC were registered until now. Currently, there is only one active study recruiting patients (Clinical Trial Identifier: NCT02484404). However, as a single agent or in combination with standard systemic therapies, iPARP did not demonstrate promising activity so far (Clinical Trial Identifiers: NCT00912743, NCT02305758), probably because PARP inhibition is not enough to disrupt BER pathway in dMMR tumors treated with 5-FU based schemes and provoke the expected synthetic lethality. However, in *MGMT* hypermethylated and dMMR colorectal tumors, the association of iPARP with 5-FU-based treatments or TMZ may favor patients' outcomes.

In terms of CRC prognosis, PARP-1 levels were reported to be higher in comparison to normal colon and in polyp tissues, suggesting an influence in CRC disease progression (Dziaman et al., 2014b). In addition, overexpression of PARP-1 in tumor tissues has been associated with less aggressive tumors, with proximal localization and absence of lymphatic and perineural invasions (Leguisamo et al., 2017; Santos et al., 2014). Unfortunately, PARP-1 levels still do not present relation with tumor stage at the time of diagnosis (Alhadheq et al., 2016; Santos et al., 2014; Sulzyc-Bielicka et al., 2012). Two studies have assessed the prognostic value of PARP-1 expression, but only one reached significance to support that increased PARP-1 expression is a predictor of shorter OS and PFS in CRC patients (Alhadheq et al., 2016).

5.5. XRCC1

XRCC1 (X-Ray Repair Complementing Defective Repair In Chinese Hamster Cells 1) is a protein part of the BER repair pathway that interacts with human polynucleotide kinase (PNK), POLβ and DNA ligase III, which is thought to act as a scaffold in the removal alien bases, caused by ionizing radiations and alkylating agents (Brem and Hall, 2005). XRCC1 has been studied in CRC patients treated with FOLFOX-4 chemotherapy with aim to determine failure to treatment with no significant difference about its expression (Huang et al., 2013). However, high expression of this protein has been correlated with high grade tumors (Leguisamo et al., 2017) and lymphatic invasion, lymph node metastasis and higher stages (Azambuja et al., 2017).

5.6. BER conclusions

Despite the growing body of experimental data regarding BER participation in CRC development and response to chemotherapy, there is still a lack of evidence for the use of BER genes and protein levels as a prognostic and predictive factors (Table 4). Furthermore, targeting this pathway as a therapeutic approach in CRC has not been thoroughly explored. Indeed, considering that alkylating agents' cytotoxicity is favoured by the inefficiency of MGMT, MMR and BER, the number of studies exploring the last pathway in CRC is still insufficient. Consequently, the search for a molecular signature that includes MGMT methylation and MMR status, and search for BER imbalance may be the next step to consolidate the use of new approaches such as alkylating agents and iPARP in refractory CRC.

6. Nucleotide excision repair: the prognostic and predictive value of NER is represented by ERCC1 and ERCC2

The nucleotide excision repair (NER) machinery is involved in repairing a great variety of DNA lesions, such as pyrimidine dimers, bulky DNA adducts and intrastrand DNA cross-links, which all distort the DNA double helix. The classic NER pathway involves roughly 30 proteins operating in a coordinated manner. NER proceeds through a series of steps, starting with damage recognition, DNA uncoiling, incision and removal of the DNA strand around the damage, and lastly, DNA synthesis and ligation (Spivak, 2016). In addition to global genome repair (GG-NER), NER maintains a specialized pathway, termed transcription-coupled NER (TC-NER), which specifically deals with lesions on the transcribed strand of DNA that blocks RNA polymerase progression. These two NER pathways are thought to differ only at the lesion recognition step, but utilize common machinery to execute the

Table 4
Prognostic value of ERCC1 low and ERCC2 high gene/protein expression in colorectal cancer. All patients were treated with oxaplatin based therapy.

Pathway component	n	Product	Clinicopathological feature association	p	Survival		p	Author
ERCC1 low expression	50	mRNA	NE		OS (months)*	10.2 [CI 7.8–15.1] vs. 1.9 [CI 1.1–4.9]	< 0.001(3)	Shirota et al. (2001)
	168	protein	NE		OS (months)*	16 vs. 25	< 0.01(3)	Chang et al. (2009)
					PFS (months)*	9 vs.13	< 0.01(3)	
	119	mRNA	NE		OS (months)*	33.1 vs. 16	0.025(3)	Grimminger et al. (2012)
	255	protein	Stage III and IV	< 0.001(1)	NE			Li et al. (2013)
	180	protein	NE		OS	Worse	< 0.001(3)	Huang et al. (2013)
					PFS	Shorter	< 0.001(3)	
	120	mRNA	N+	< 0.001(2)	OS	Worse	< 0.001(3)	Yuanming et al. (2013)
			Stage III and IV		PFS	Shorter	< 0.001(3)	
	56	protein	NE		OS (months)*	30.9 vs. 13.2	0.021(3)	Han et al. (2014)
	895	protein	NE		DFS (HR)	0.378 [CI 0.316–0.451]	< 0.001 (4)	Zhang et al. (2015a,b)
					OS (HR)	0.375 [CI 0.307–0.458]	< 0.001(3)	
	41	mRNA	NE		OS (months)*	36 vs. 10.1	< 0.001(3)	Choueiri et al. (2015)
	64	mRNA	NE		OS (HR)	2.019 [CI 0.875–4.661]	0.1(1)	Kassem et al. (2017)
					EFS (HR)	3.088 [CI 1.399–6.819]	0.005(1)	
	86	mRNA	NE		DFS (months)*	51.9 ± 1.4 vs. 38.4 ± 3.2	0.002(3)	Huang et al. (2017)
					OS (months)*	53.1 ± 0.9 vs. 40.6 ± 3.4	0.005(3)	
	2233	protein	M+	0.028(1)	OS (HR)	0.82 [CI 0.65–1.04]	0.11(3)	Li et al. (2016)
ERCC2 high expression	64	mRNA	NA		OS (HR)	1.363 [CI 0.592–3.138]	0.467(5)	Kassem et al. (2017)
					EFS (HR)	1.621 [CI 0.78–3.369]	0.195(5)	
	86	mRNA	NE		DFS		0.567(2)	Huang et al. (2017)
					OS		0.539(2)	

final steps of the repair response (Spivak, 2015).

Classically, NER is involved in the repair of photoproducts caused by UV light (cyclobutane pyrimidine dimers and 6-4 pyrimidine-pyrimidones - CPD and 6-4-PP, respectively), but its scope of action is much wider, since it involves the repair of adducts resulting from numerous toxic agents, such as cigarette smoke and chemotherapeutic drugs, especially those derived from platinum and nitrosurea.

Despite NER is not classically involved with the repair of oxidative lesions, an interaction with BER pathway may suggest new roles for this pathway, especially in colorectal carcinogenesis. For example, CSA and CSB (Cockayne Syndrome A and B) proteins (TC-NER) have been shown to stimulate the activity of Neil1 and APE1 and/or to directly affect OGG1 transcription (Parlanti et al., 2012) and PARP-1 activity (Thorslund et al., 2005; Melis et al., 2013; D'Errico et al., 2013). In addition, both XPG (TC-NER) and XPC (GG-NER) also appear to play a role in the repair of oxidative lesions that distort the double helix through recognition and functioning as a cofactor to DNA glycosylases (Melis et al., 2013).

NER prognostic value is significantly more studied than its predictive in CRC (Table 5). However, it is totally conceivable that alterations in this pathway may have a contribution in colorectal carcinogenesis, since the key exogenous risk factors (e.g., smoking, alcohol consumption, high consumption of processed red meat and saturated fat) are responsible for generating reactive compounds that comprimise the DNA integrity. Indeed, CRC tissues have increased NER-specific DNA repair capacity in relation to matched normal tissues (Herrera et al., 2009; Slyskova et al., 2012), which points out to a transitory cellular effort to reduce the amount of damage in these tissues during the carcinogenic process (Jonsson et al., 2010). Yet, no study has been able to find evidence of a determinant role for NER imbalance in colorectal carcinogenesis so far. This fact may indicate that this pathway is not a contributing factor to malignant transformation but that it ensures some growth advantage in the existing tumor, reducing its vulnerability to accumulation damage to DNA that precedes cell death. In this context, it is possible that the tumor genetic stability given by the increased activity of DNA repair effectors is actually associated with the metastatic process (Sarasin and Kaufmann, 2008).

In addition, oxaliplatin composes the FOLFOX scheme and is one of the main agents used in the treatment of CRC for patients diagnosed with TNM stage III and IV. Like other platinum-based compounds, oxaliplatin exerts its cytotoxic effect mostly through DNA damage. This platinum agent causes bulky DNA adducts classically repaired by the NER pathway (Alcindor and Beauger, 2011; Reardon et al., 1999) In vitro, despite initial sensitivity to oxaliplatin, most cancer cells will ultimately develop resistance. For example, cells that overexpress ERCC1 are resistant to oxaliplatin (Arnould et al., 2003), which demonstrates NER influence in CRC platinum-based response to treatment and may have predictive value by indicating individual patient response to oxaliplatin.

6.1. *ERCC1 as prognostic and predictive biomarkers*

ERCC1 complexes to ERCC4 (excision repair cross-complementation group 1 and 4, respectively) to make the incision at the 3′ end of the damaged site during NER common pathway. As aforementioned, ERCC1 overexpression has been associated not only to resistance to cisplatin-based chemotherapy, but also to better outcomes in CRC patients without treatment. Currently, ERCC1 expression is used as a predictive biomarker for therapy response (Bohanes et al., 2011; Schirripa and Procaccio, 2017).

The first study on this regard included 50 patients and described the relationship between *ERCC1* gene expression and survival in 5-FU–resistant mCRC treated with FOLFOX, suggesting that low *ERCC1* mRNA levels was a prognostic biomarker for better overall 5-years survival (10.2 [CI 7.8–15.1] vs. 1.9 [CI 1.1–4.9] months, $p < 0.001$) (Shirota et al., 2001). Since then, eleven studies were conducted to confirm the impact of the changes in ERCC1 gene and protein expression in CRC patients' clinical outcomes and response to treatment. However, in terms of clinicopathological outcomes, only three studies reported that ERCC1 low expression are indicative of tumor aggressiveness, by associating ERCC1 low expression to higher stage tumors and presence of lymph node and distant metastasis (Li et al., 2013; Yuanming et al., 2013; Li et al., 2016).

Currently, it is possible to consider ERCC1 the most promising predictive biomarker in patients with CRC treated with oxaliplatin in combination with a pyrimidine analog such as 5-FU or capecitabine. In

Table 5
Studies evaluating the predictive value of low ERCC1 and high ERCC2 gene/protein expression in CRC patients.

	n	Product	Disease stage	Treatment	Primary endpoint	*p*	Conclusions	Author	
ERCC1 low expression	45	mRNA	IV	Oxaplatin and Fluoracil	Response to therapy		0.29(1)	Primary endpoint not met	Shirota et al. (2001)
	25	mRNA	IV	Oxaliplatin and Capecitabine	TTF (days)	162 vs. 85*	0.046(2)	Primary endpoint met in CRC harboring ERCC1 low expression	Uchida et al. (2008)
	59	mRNA	IV	*First-line*	OS (HR)			Primary endpoint met in FOLFOX isolated treated-CRC with low ERRC1 expression	Grimminger et al. (2012)
				FOLFOX		0.27 [CI 0.09–0.85]	0.025(3)		
				FOLFOX + PTK		2.95[CI 0.8–10.8]	0.1(3)		
	63			*Second-line*		0.38 [CI 0.16–0.92]			
				FOLFOX			0.03(3)		
				FOLFOX + PTK		1.05[CI 0.35–3.17]	0.94(3)		
	160	protein	III	FOLFOX/XELOX	OS (HR)	2.44 [CI 1.37–4.34]	0.02(2)	Primary endpoint met in FOLFOX/XELOX treated-CRC with low ERRC1 expression	Li et al. (2013)
					DFS (HR)	1.98 [CI 1.19–3.31]	0.009(2)		
	95			5-FU	OS (HR)	1.16 [CI 0.63–2.14]	0.62(2)		
					DFS (HR)	1.16 [CI 0.63–2.14]	0.62(2)		
	160	protein	III	FOLFOX	Early failure to therapy (HR)	5.153 [CI 1.654–16.057]	0.005(4)	Primary endpoint met in FOLFOX treated CRC with low ERRC1 expression	Huang et al., 2013
	86	protein	II-IV	FOLFOX and radiotherapy	Response to therapy (HR)	9.397 [CI 2.721–32.457]	< 0.0001(4)	Primary endpoint met in FOLFOX and radiotherapy treated CRC with low ERRC1 expression	Huang et al. (2017)
ERCC2 high expression	160	protein	III	FOLFOX	Early failure to therapy (HR)	1.074 [CI 0.462–2.497]	0.869(2)	Primary endpoint not met	Huang et al., 2013
	86	mRNA	II-IV	FOLFOX and radiotherapy	Response to therapy (HR)	0.53 [CI 0.151–1,855]	0.32(2)	Primary endpoint not met	Huang et al. (2017)

FOLFOX: Leucovorin + 5-Fluorouracil + Oxaplatin; XELOX: Capecitabine + Oxaplatin; 5-FU: 5-Fluorouracil; PTK - anti-VEGF/VEGF based therapy; OS: overall survival; DFS: disease free survival; TTF: time to treatment failure; (HR): hazard ratio; CI: confidence interval; *: low vs high ERCC1; (1): fisher's exact test; (2): log-rank; (3): cox regression; (4): multivariate.

Table 6
Double Strand Break Repair components as prognostic biomarkers in CRC patients.

Pathway component	n	Product	Clinicopathological feature association	*p*	Clinical outcome			*p*	Author
ATM	low expression	320	protein	NA		OS a	Worse	0.0097(4)	Grabsch et al. (2006)
		445	protein	NA		OS		NS(3)	Beggs et al. (2012)
						DFS(HR)a	1.67 [CI 1.11–2.5]	0.015(3)	
		112	mRNA	N+	< 0.001(1)	OS(HR)a	2.764 [CI 1.226–7.422]	0.027(3)	Lu et al. (2014)
				Stage III and IV	< 0.001(1)	DFS(HR)a	2.16 [CI 1.108–5.624]	0.011(3)	
		67	mRNA	high grade tumours	0.013(2)	NE			Xiong and Zhang (2017)
BAP1	low expression	252	protein	T3 and T4	0.001(3)	OS	Worse	< 0.001(4)	Tang et al. (2013)
				N+	0.003(3)				
				M+	< 0.001(3)	DFS	Worse	< 0.001(4)	
				high grade tumours	0.004(1)				
BRCA1	low expression	322	protein	NA		OS	Worse	0.0049(4)	Grabsch et al. (2006)
						DFS	Worse	0.0261(4)	
		120	mRNA protein	N+	< 0.001(3)	OS (HR)a	2.844 [CI 1.106–7.44]	0.021(3)	Yuanming et al. (2013)
				Stage III and IV	< 0.001(3)	PFS (HR)a	2.401 [CI 1.115–5.722]	0.013(3)	
		78	mRNA	NE		OS (HR)a	0.836 [CI 0.764–0.915]	< 0.001(2)	Abdul Aziz et al. (2016)
		466	mRNA	NA		OS	Worse	0.001787(4)	Liu and Zhang (2017)
BRCA2	low expression	282	protein	high grade tumours	0.018(3)	OS		NS(4)	Grabsch et al., 2006
		422	protein	high grade tumours	< 0.001(3)	OS	Worse	< 0.001(4)	Wang et al. (2018)
γ-H2AX	low expression	207	protein	Dukes C tumours	0.038(3)	DFS (HR)a	0.84 [CI 0.42–1.68]	0.63(3)	Beggs et al. (2012)
Ku70	high expression	96	protein	T3 and T4	0.022(3)	DFS	Worse	0.0057(4)	Komuro et al. (2002)
	low expression	207	protein	NA		DFS (HR)a	0.78 [CI 0.4–1.54]	0.477(3)	Beggs et al. (2012)
		120	mRNA	N+	< 0.001(1)	OS	Worse	< 0.001(4)	Lu et al. (2014)
				Stage III and IV	< 0.001(1)				
		152	mRNA	N+	< 0.001(1)	OS	Worse	< 0.001(4)	Lu et al. (2015)
				Stage III and IV	< 0.001(1)				
Ku86	low expression	96	protein	NA		DFS	Better	0.022(4)	Komuro et al. (2002)
MRE11	low expression	625	mRNA	proximal tumour	< 0.001(3)	OS (%)a,b	67 vs. 59	0.0005(4)	Pavelitz et al. (2014)
				high grade tumours	< 0.001(3)	DFS (%)a,b	68 vs. 71	0.0038(4)	
		78	protein	NA		PFS		NS(4)	Ihara et al. (2016)
RAD51	high expression	1213	protein	NA		OS	Worse	0.013(4)	Tennstedt et al. (2013)
		78	protein	NA		PFS	Worse	0.035(4)	Ihara et al. (2016)
		54	protein	high grade tumours	0.006(2)	OS	Worse	< 0.05(4)	Li et al. (2016)
				N+	0.002(2)				
XRCC2	high expression	153	mRNA	high grade tumours	0.028(2)	NE			Xu et al. (2014)
		100	mRNA	T3 and T4	0.024(1)	OS	Worse	0.01(4)	Qin et al. (2015)
		101	mRNA	T3 and T4	0.009(2)	PFS	Worse	< 0.001(4)	Zhang et al. (2017)
				N+	0.021(2)				
				M+	0.01(2)	OS	Worse	0.0053(4)	
				Stage III and IV	0.001(2)				

Table 7
Double strand break repair components and its influence in CRC response to treatment.

Pathway component		Product	n	n Disease Stage	Treatment	Primary endpoint	p	Conclusions	Author
ATM	protein	33	I-IV	Adjuvant CT + RT	DFS		0.0046(1)	Primary endpoint met in CRC harboring ATM high expression	Grabsch et al. (2006)
BRCA1	protein	34	I-IV	Adjuvant CT + RT	DFS OS		0.0049(1) 0.0261(1)	Primary endpoint met in CRC harboring BRCA1 high expression	Grabsch et al. (2006)
Ku70	protein	96	I-III	RT	ORR(%)*	77 vs. 41	< 0.001(2)	Primary endpoint met in CRC harboring Ku70 low expression	Komuro et al. (2002)
Ku86	protein	96	I-III	RT	ORR(%)*	73 vs. 45	0.012(2)	Primary endpoint met in CRC harboring Ku86 low expression	Komuro et al. (2002)
MRE11	mRNA	320	III	5-FU/LV	DFS(%)* OS(%)*	67 vs. 61 70 vs. 73	NS	Primary endpoint not met	Pavelitz et al. (2014)
		305		Irinotecan + FU/LV	DFS(%)* OS(%)*	67 vs. 57 67 vs. 69			
XRCC2	mRNA	67	I-IV	RT	ORR(%)	72 vs. 21	0.0002(3)	Primary endpoint met in CRC harboring XRCC2 low expression	Qin et al. (2015)
	mRNA	97	III-IV	FOLFOX	ORR(%)	70 vs.20	< 0.001(3)	Primary endpoint met in CRC harboring XRCC2 low expression	Zhang et al. (2017)

CT: chemotherapy; RT: radiotherapy; 5-FU: 5-Fluoracil; LV: Leucovorin; OS: overall survival; DFS: disease free survival; ORR: overall response rate (complete and partial response); *low expression vs. high expression; (1): log-rank; (2): univariate (3): chi-squared test; NS: not signifance.

eleven studies investigating the ERCC1 gene expression in CRC tumors treated with oxaliplatin, nine have found that patients whose tumors harbored low ERCC1 expression had better overall survival (Chang et al., 2009; Choueiri et al., 2015; Grimminger et al., 2012; Han et al., 2014; Kassem et al., 2017; Shirota et al., 2001; Zhang et al., 2015b; Huang et al., 2017; Li, 2017; Huang et al., 2013; Yuanming et al., 2013) (Table 5). Four studies were performed in patients with stage III CRC and the others in metastatic patients. Even with different methods used to measure ERCC1 expression and different cut-off values, the results were significant. Six studies analyzed the association between PFS or DFS and ERCC1 expression. These studies were able to establish that ERCC1 overexpression is a predictor of shorter PFS in CRC patients that received oxaliplatin in combined chemotherapy regimens (Chang et al., 2009; Huang et al., 2013; Yuanming et al., 2013; Zhang et al., 2015a,b; Kassem et al., 2017; Huang et al., 2017).

Regarding ERCC1 expression and response to treatment, its overexpression was associated with early failure to treatment defined as local recurrence or distant metastasis 1 year after XELOX (capecitabine, leucovorin and oxaplatin) (Uchida et al., 2008) and FOLFOX (oxaliplatin and capecitabine) regimens (Huang et al., 2013). Overexpression of ERCC1 was also correlated to poor response to therapy (Huang et al., 2017). When comparing CRC patients treated with FOLFOX or FOLFOX with anti-VEGF based therapies, low ERCC1 expression in neoplastic tissues was a predictor of better overall survival in FOLFOX isolated first and second-line treated patients (Grimminger et al., 2012). Low ERCC1 predictive value was also demonstrated in patients treated with FOLFOX/XELOX in comparison to the ones treated with 5-FU as a single agent (Li et al., 2013).

6.2. ERCC1 conclusion

ERCC1 is a non–guideline-endorsed genomic test, but it is mentioned by the NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) for use in patients with CRC (NCCN, 2017; Schirripa and Procaccio, 2017). In clinical practice, oncologists have started to require information on ERCC1 expression on CRC tumors since its overexpression strongly suggests resistance to platinum chemotherapy but also favorable prognosis (Gray et al., 2017). Conversely, ESMO consensus guidelines for the management of patients with mCRC do not recommended the use of ERCC1 protein levels for treatment decisions involving the use of oxaliplatin in routine practice (Van Cutsem et al., 2016), probably because none of the published reports had a proper study design, including intention-to-treat population and evaluation of ERCC1 sensibility and specificity. Thus, to include ERCC1 expression as a predictive biomarker to response to oxaliplatin-based treatments, studies of diagnostic accuracy are mandatory.

6.3. ERCC2

ERCC2 (Excision Repair Cross-Complementing 2), also known as XPD (Xeroderma Pigmentosum Group D), is a subunit of human transcriptional initiation factor with ATP-dependent helicase activity and participates in DNA unrolling during NER. ERCC2 prognostic or predictive role in CRC is much less studied than ERCC1. Nevertheless, increased levels of ERCC2 have also been associated with resistance to oxaliplatin therapy in CRC patients (Huang et al., 2008). Two studies failed to prove the predictive role of ERCC2 expression for stage II−IV CRC patients treated with FOLFOX-4 adjuvant chemotherapy (Huang et al., 2013) or in association with radiotherapy (Huang et al., 2017). Regarding the prognostic value of ERCC1 expression in CRC, no difference in overall survival and event free survival of patients whose tumors harbored ERCC2 overexpression were found (Huang et al., 2017; Kassem et al., 2017).

7. Double Strand Break Repair: the pathway with few studies that needs more attention

The DNA double-strand breaks are considered an important source of DNA lesion that leads to genetic alteration, chromosomal instability, and ultimately malignant transformation. Human cells have two pathways of repair DSB: homologous recombination (HR) and non-homologous end joining (NHEJ). Tables 6 and 7 summarize the main studies relating DSB repair as prognostic or predictive biomarkers in CRC patients, respectively.

7.1. Homologous recombination

7.1.1. ATM

ATM (Ataxia Telangiectasia Mutated) is a serine-threonine kinase that is triggered by DSBs and activates several downstream targets, including those involved in DNA repair, and may also induce senescence and apoptosis (Beggs et al., 2012). Reduced ATM expression was reported as biomarker of poor disease-free survival with poor response and early failure after adjuvant chemotherapy and radiotherapy treatments (Grabsch et al., 2006). When clinicopathological data was analyzed, decreased ATM expression was significantly associated with advanced TNM stage (Lu et al., 2014) and high grade tumors (Xiong and

Zhang, 2017). Low ATM expression was also associated to poorer overall survival and disease-free survival in CRC patients (Beggs et al., 2012; Grabsch et al., 2006; Lu et al., 2014).

7.1.2. BRCA1 and BRCA2

BRCA1 (Breast Cancer Susceptibility Gene 1) is a 91KD nuclear-localized deubiquitinating enzyme and has been involved in various biological processes including chromatin dynamics, DNA damage response, and regulation of the cell cycle and cell proliferation. Although studies in the past reported an increased risk of CRC in patients with BRCA1 or BRCA2 germ-line mutations (Brose et al., 2002; Kirchhoff et al., 2004; Niell et al., 2004; Risch et al., 2001), other studies aimed to achieve the importance of BRCA1 in sporadic CRC patients and response to therapy. Recently, reduced expression of BRCA1 and BRCA1-associated protein 1 (BAP1) were associated with poor prognosis of CRC (Abdul Aziz et al., 2016; Liu and Zhang, 2017; Lu et al., 2014; Tang et al., 2013) and more aggressive tumors (Tang et al., 2013; Yuanming et al., 2013). CRC patients whose tumors overexpressed BRCA1 and were treated with adjuvant chemotherapy and radiotherapy presented better overall survival and disease-free survival (Grabsch et al., 2006). Decreased BRCA2 expression in colorectal tumors was associated with high grade tumors and poorer overall survival (Grabsch et al., 2006; Wang et al., 2018).

7.1.3. γ-H2AX

γ-H2AX is a product of histone H2AX phosphorylation form carboxyl terminus and it is a sensitive marker for DNA double-strand breaks, which may lead to cancer or apoptosis (Ward and Chen, 2001). Using γH2AX detection to determine the extent of DSB induction may help to detect precancerous cells, to stage cancers, monitor the effectiveness of cancer therapies and develop novel anticancer drugs (Bonner et al., 2008). Regarding CRC, only one study reported γH2AX low expression association with more advanced tumors, but with no impact in patients' disease free survival (Beggs et al., 2012).

7.1.4. MRE11 and RAD51

MRE11 is one of the enzymes required to form the core of the MRN (MRE11-RAD50-NBS1) complex. The importance of MRE11 downregulation in CRC prognosis was evaluated in two studies, but only one found association with features of tumor aggressiveness (proximal and high grade tumors) and poor overall and disease free survival in a subset of stage III CRC patients (Pavelitz et al., 2014). Other study with MRE11 showed that no significant association was identified between MRE11 expression and PFS (Ihara et al., 2016). In addition, no predictive value was found for changes MRE11 expression in colorectal neoplasms so far (Pavelitz et al., 2014).

RAD51 has essential roles in detection, signaling, protection and repair of DSBs and acts as the central catalyst of the error-free HR repair (Ibrahim et al., 2011). Recently, its protein overexpression in CRC patients was associated with presence of lymph node metastasis (Li et al., 2016) and poor overall and disease free survival (Tennstedt et al., 2013; Ihara et al., 2015; Li et al., 2016). No study has evaluated RAD51 predictive value in CRC.

7.1.5. XRCC2

In the HR pathway, XRCC2 protein (X-Ray Repair Complementing Defective Repair in Chinese Hamster Cells 2) is a key factor and contributes to the DNA DSBs repair and probably its expression is involved in either initiation or progression of tumorigenesis. In clinicopathological studies its overexpression is associated with more aggressive tumors (Qin et al., 2015; Xu et al., 2014; Zhang et al., 2017) with worse overall survival (Qin et al., 2015; Zhang et al., 2017). CRC patients with low *XRCC2* mRNA levels presented better overall response rate after radiotherapy (Qin et al., 2015) and chemotherapy with FOLFOX (Zhang et al., 2017) treatments.

7.2. Non-homologous end joining

NHEJ is a pathway that, in order to guarantee the DNA molecule integrity, repairs DSBs without requiring a template. NHEJ uses short DNA sequences called microhomologies to guide repair the most accurately as possible. These microhomologies are often present in single-corded protrusions at the ends of DSB. Inadequate NHEJ leads to translocations and telomere fusion, which are hallmarks of tumor cells (Espejel et al., 2002; Budman and Chu, 2005). This mechanism involves the formation of a 70 kDa protein (Ku70) and a 86 kDa protein (Ku86) protein heterodimer with a DNA-dependent protein kinase C to the site of DNA damage (Grabsch et al., 2006). This heterodimer may have potential as a predictive assay for tumor radiosensitivity due to its involvement in the recognition or repair of radiation-induced DNA damage (Komuro et al., 2002). Downregulation of Ku70 was associated with poor disease-free survival, overall survival, lymphnodes invasion and advanced CRC tumors and loss of Ku70 might act as a biomarker to predict poor prognosis in patients with CRC (Komuro et al., 2002; Lu et al., 2014, 2015). Low expression of Ku86 in patients with rectal carcinoma and treated with radiotherapy were associated with better overall survival (Komuro et al., 2002).

7.2.1. DSB repair conclusion

In sum, reduced ATM expression was an independent prognostic biomarker of poor disease-free survival and overall survival and predict poor response to the therapy with early failure in CRC patients. Reduced expression of BRCA and BAP1 were also associated with more aggressive tumors, but conflicting results about its prognostic role impedes a conclusion. XRCC2 overexpression is related to more aggressive tumors with poor response to therapy and worse survival and progression-free disease. On its turn, NHEJ is represented by Ku70 and Ku86 and low expression of these proteins seems to positively affect prognosis and survival in CRC patients treated with radiotherapy.

8. Translesion synthesis: a new horizon in DNA repair and CRC

DNA replication in normal cells is regulated by mechanisms that ensure that it occurs only once per cycle. The replication and maintenance of the genome are absolute requirements for life. A proliferating cell must duplicate its entire complement of DNA with excellent precision, facing all kinds of setbacks (such as deleterious endogenous and environmental genotoxic agents), as well as the intrinsic chemical instability of the DNA molecule itself. (Hanawalt, 2007; Kunkel, 2003).

Translesion synthesis (TLS) is a mechanism that allows the DNA to continue to replicate even in the presence of lesions that would otherwise disrupt the process. This pathway is intended to tolerate the lesions for the maintenance of DNA replication and cell division by impeding replication fork stalling and preventing cell cycle arrest or induction to apoptosis. When a high-fidelity DNA polymerase encounters a lesion during the replicative process, it may be replaced by a low-fidelity 'translesion' one, which is capable of synthesizing DNA despite the presence of the lesion. After it has passed the replication fork the single-strand gap is repaired using template DNA on a sister chromatid, similar to the process used during homologous recombination (Waters et al., 2009; Lord and Ashworth, 2012).

Fifteen mammalian DNA polymerases have been identified and they have functions in the replication of genomic DNA, but the majority have an important role in the DNA repair. DNA polymerases are part of BER, NER, HR and NHEJ pathways, performing the synthesis of a new DNA strand or binding to DNA breaks (Lange et al., 2011). Among DNA polymerases, replicative polymerases are specific for undamaged DNA bases, but have little replication capacity when a lesion is encountered; in counterpart, translesion DNA polymerasesas Polη (PolH), Polκ (PolK), Polι (PolI) and REV1 (family Y), Polζ (family B) and Polθ (PolQ) and Polν do not have proofreading or exonuclease activities. Thus, in

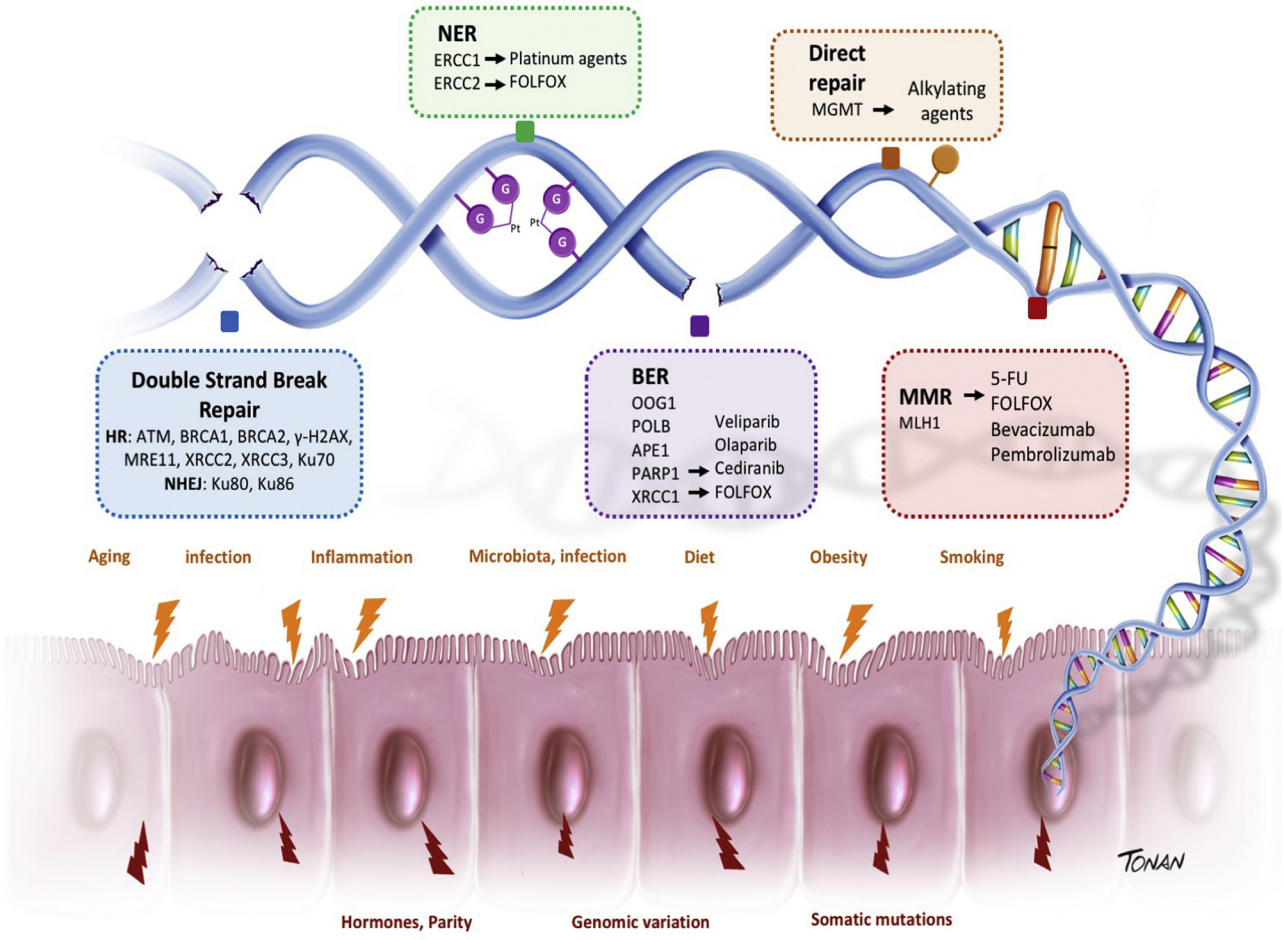

Fig. 1. The main DNA repair genes involved in colorectal cancer as prognostic or predictive biomarkers.

Table 8
Summarized role of the main DNA repair components expression with potential value as prognostic and/or predictive biomarkers in sporadic CRC.

Pathway	Component	Number of studies included*		Expression	Prognosis	Number of studies supporting	Response to treatment	Number of studies supporting
DR	**MGMT**	19	Decreased or lost	More advanced and aggressive tumors	5	Alkylating agents	Partial response with no improvement in PFS	4
				Worse OS	2	Irinotecan	Better PFS	1
BER	**OGG1**	3	Decreased	More aggressive tumors	3	Unknown		1
				No prognostic value	1			
	MPG	2	Increased	More aggressive tumors	2	Unknown		0
				Shorter PFS	1			
	POLB	3	Increased	More aggressive tumors	4	Unknown		0
				Shorter OS	1			
	PARP1	5	Decreased	More aggressive tumors	3	Unknown		0
				Worse OS and PFS	2			
	XRCC1	4	Increased	More aggressive tumors	2	FOLFOX	No predictive value	1
				No prognostic value	1			
NER	**ERCC1**	13	Decreased	More advanced tumors	3	Oxaliplatin based	Better ORR, PFS and OS	5
				Better OS and PFS	9			
	ERCC2	3	Increased	No prognostic value	0	FOLFOX + RT	No predictive value	2
					2			
DSBR	**ATM**	4	Decreased	More aggressive tumors	2	Adjuvant CT + RT	Early failure	1
				Poorer OS and PFS	2			
	BRCA1	4	Decreased	More aggressive tumors	1	Adjuvant CT + RT	Early failure	1
				Confliciting results	2			
	Ku70	4	Decreased	More aggressive tumors	2	RT	Better OS and PFS	1
				Worse OS and PFS	2			
	XRCC2	3	Increased	More aggressive tumors	3	RT	Poorer ORR	1
				Worse OS and PFS	2	FOLFOX		1

DR: direct repair; BER: base excision repair; NER: nucleotide excision repair; DSB: double strand break repair; *studies that evaluate gene or protein expression in colorectal neoplasms; FOLFOX: Leucovorin + 5-Fluorouracil + Oxaplatin; CT: chemotherapy; RT: radiotherapy; PFS: progression free survival; ORR: overall response rate (complete and partial response); OS: overall survival.

the context of TLS, these DNA polymerases are not considered DNA repair enzymes, but tolerance factors of DNA damage. Therefore, this process is considered error-prone, because lower fidelity polymerases can incorporate wrong nucleotides to the DNA, being able to cause alterations in the sequence of DNA that can lead to mutations (Cazaux, 2010).

One study monitored the levels of DNA polymerases expression in patients with colorectal and breast cancers. Overexpression of *POLK gene* were observed in both diseases, especially in patients with more aggressive subtypes of breast cancer (Lemée et al., 2007). In the same study, the authors noted that the excess of *POLQ* in breast cancer was associated with worse prognosis, demonstrating that the upregulation of an error-prone polymerase may represent a new prognostic marker (Lemée et al., 2007). Increased expression of Polθ protein was also observed in stomach, lung and colon tumor tissues (Kawamura et al., 2004). In CRC patients, overexpression of Polθ was associated with lower survival rates (Pillaire et al., 2010). Recently, another study suggested that the induction of oxidative stress, chromosomal breaks and abnormalities observed in cells with overexpression of Polθ could be a strong contributor to the genetic instability that accompanies the development of cancer in these tissues (Cazaux, 2010). In fact, more recently, it was shown that Polθ is involved with BER pathway and processes AP sites by inserting an adenine residue and extending the polymerization, also exhibiting 5′-deoxyribose-phosphate lyase activity (Wood and Lange, 2014; Yousefzadeh et al., 2014). This fact considers TLS in CRC response to 5-FU-based chemotherapy (Matuo et al., 2010).

Polη is responsible for a variant of Xeroderma Pigmentosum (XP-V), a rare autosomal recessive disorder. Affected patients present an extreme sensitivity to light and an extremely high incidence of skin cancer. However, in contrast to other types of Xeroderma Pigmentosum, XP-V cells have proficient NER, but are unable to perform the translesion synthesis of the cyclobutane dimer of thymidine. Even though Polη has the ability to efficiently replicate the pyrimidine dimer, such enzyme is absent in patients altered affected by this disorder. (Cazaux, 2010).

As for Polκ, it has the ability to perform the TLS of adducts such as benz[*a*]pirene, and seems to have a function in the synthesis step in NER (Bétous et al., 2009). In CRC, low levels of Polκ in tumor tissue were observed (Lemée et al., 2007). Polκ was also implicated in the bypass of alkylated bases and abasic sites, in addition to being implicated in the extension of mispairing and small lesions to DNA(Lupari et al., 2012).

In summary, only one study conducted showed that overexpression of Polθ is related to a lower survival rate in CRC patients. This pathway is an opening for future clinical DNA molecular repair studies, with the objective of determining new prediction and predictive biomolecular factors.

9. Conclusion

Colorectal cancer staging still lacks the use of molecular biomarkers for both disease prognosis and therapeutic decision, which leads to disease misclassification and incorrect treatment. In this context, DNA repair-based molecular biomarkers may be a decisive tool in the diagnostic and therapeutic approach for colorectal cancer (Fig. 1). The growing body of evidence of changes in DNA repair components in the CRC progression and response to chemotherapy strengthen their potential as prognostic and predictive tools (Table 8). Nevertheless, proper diagnostic and randomized clinical trials must be conducted to ensure technical quality and clinical accuracy. Currently, the MMR pathway status and ERCC1 (NER) are turning into the most relevant predictive and prognostic biomarkers, which can be implemented in the clinical practice to tailor the chemotherapy regimens in CRC patients. Indeed, the use of both MMR status and ERCC1 protein expression are currently suggested by ESMO and NCCN for this purpose. Recently, the use of PARP1 inhibitors is achieving certain significance in the CRC treatment scenario, mainly based on the rational of synthetic lethality in dMMR tumors. However, no definitive results were found so far. Likewise, the direct repair pathway functionality (represented by MGMT expression), has been studied regarding its response to alkylating agents, such as temozolomide, and its correlation with partial response but without improvement in progression-free survival, which still requires further studies to define its true importance in the treatment of CRC. Finally, there are also promising new data regarding the involvement of MPG and other BER proteins, which imbalance in CRC tumors correlates with poor clinical and pathological outcomes. Other DNA repair pathways such as DSB repair and TLS still need more attention from the scientific community to define its real role in CRC carcinogenesis and its potential as prognosis biomarkers.

Conflict of interest

The authors declare that there are no conflicts of interest.

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