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Emerging paradigms in the treatment of liver metastases in colorectal cancer

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ABSTRACT

Efforts to combat colorectal cancer have benefited from improved screening and surveillance, which facilitates early detection. The survival rate associated with diagnosis at stage I is approximately 90%. However, progress in improving survival in metastatic colorectal cancer (mCRC) has been minimal. This review focuses on mCRC with special emphasis on the molecular aspects of liver metastases, which is one of the most frequently involved organ site. Better molecular evidence is required to guide the decisions for surgical and other interventions used in the clinical management of mCRC. Results from different treatment modalities have exposed significant gaps in the existing paradigms of the mCRC management. Indeed there is a critical need to better understand molecular events and pathways that lead to colorectal cancer liver metastasis. Such a focused approach may help identify biomarkers and drug targets that can be useful in the clinical applications. With this focus, we provide an account of the molecular pathways involved in the spread of CRC to the liver. Specifically, the molecular changes at the DNA and RNA levels that are associated with liver metastases are discussed. Similarly, we describe relevant microRNAs that are identified as regulators of gene expression and can also serve as biomarkers. Conventionally applied biomarkers are not yet specific and sensitive enough to be relied in routine clinical decision making. Hence search for novel biomarkers is critically needed especially if these can be utilized using liquid biopsies. This review provides a comprehensive analysis of current molecular evidence along with potential future directions that could reshape the diagnostic and management paradigms and thus mitigate the devastating impact of colorectal cancer metastasis to the liver.

1. Introduction

Colorectal cancer (CRC) is considered the second common type of cancer among women and the third among males (Ferlay et al., 2015). The burden of CRC is significant due to poor survival outcomes that are preventable and curable at early stages. There have been extensive

Abbreviations: CRC, colorectal cancer; mCRC, metastatic colorectal cancer; CLM, colorectal liver metastases; SR, surgical resection; PVE, portal vein embolism; RFA, radiofrequency ablation; APC, adenomatous polyposis coli; LOH, loss of heterozygosity; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; CEA, carcinoembryonic antigen; TCF, T-cell factor; PTEN, phosphatase and tensin homolog; CIP2A, cancerous inhibitor of protein phosphatase 2A; Sur8, rabbit polyclonal Shoc2; RASSF, RAS-association domain family; LY2109761, TGF-β receptor type I/II (TβRI/II) dual inhibitors; YAP, yes-associated protein; Rb, retinoblastoma gene; MSI, microsatellite instability; MSS, microsatellite stability; MSI-H, high level of MSI; LASP1, LIM and SH3 domain protein 1; VEGF-B, vascular endothelial growth factor B; RKIP, Raf1 kinase inhibitor protein; MACC1, metastasis-associated gene in colon cancer-1; ctDNAs, circulating tumor DNAs; CTCs, circulating tumor cells

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efforts to understand colorectal cancer progression and associated pathways. As tumor progresses, treatment modalities for metastasis to different organs becoming challenging partly because our understanding of the molecular pathways involved in metastasis is minimal. In this review, we focus on the molecular pathways that contribute to liver metastasis in CRC. Multiple mechanisms has been studied in the progression of CRC, for example, chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI). Reviewing those pathways in the context of liver metastasis is important to assess their probable role and function in mCRC. It is extremely crucial to have better understanding of the molecular evidence to guide the treatment modalities. A focused approach may help identify biomarker and drug targets that can be useful in the clinic. We discuss the changes at the DNA and RNA levels, and the relevance of microRNAs as regulators of gene expression and as biomarker. Specific gene expression changes in mCRC are discussed. Biomarkers for different applications are not yet specific and sensitive enough to aid in clinical decision making. Hence search for novel biomarkers is needed. These biomarkers could be more valuable if they can be detected in liquid biopsies. This review provides a comprehensive analysis of current molecular evidence along with future directions that would help mitigate the devastating effect of colorectal cancer liver metastases

2. Current treatment modalities in metastatic colorectal cancer

Liver is the most common site for the spread of metastatic CRC, occurring in approximately 50% of all patients during the course of their illness. Even with the best supportive care, the median survival after hepatic spread of CRC is limited at approximately 6 months. Therefore, prompt delineation of an individualized management plan is critical for improved survival in these patients. Among a variety of available modalities, surgical resection (SR) is the standard of care as it offers the best survival benefit (Misiakos et al., 2011). All other modalities, such as chemotherapy and biologic agents, provide only a marginal survival advantage over supportive care alone. In planning for SR, multiple factors influence the strategy and the timing of the operation. The most important variables include, the site and number of metastatic lesions, single versus bilobar disease, remnant liver volume, the presence or absence of lesions close to major vessels, and whether down-staging of the lesions is necessary. The site, size and curative plan of the primary CRC are also important elements to consider in determining a plan for SR of the metastatic CRC.

For example, the surgical approach for these patients may consist of a combined resection of both primary and metastatic hepatic lesions. Alternatively, resection of the primary tumor prior to metastatic resection, and occasionally a reverse approach (i.e., hepatic resection prior to primary CRC tumor resection) can be envisioned, all yielding comparable outcomes (Brouquet et al., 2010). The reverse strategy is usually considered when hepatic-metastatic disease is relatively advanced although the primary CRC is asymptomatic. Lastly, when the hepatic spread of CRC is bilobar, a two-stage hepatic resection or a combined approach of resection plus radiofrequency ablation can be applied (Ammori and Kemeny, 2010). Since the superiority of SR was recognized in the 1980s, gradual improvements in imaging and surgical techniques have led to post-resection 5-year survival rates ranging from 40% to 58% (Vauthey et al., 2005; Artigas et al., 2007). More importantly, synergistic application of these techniques has enabled a dramatic relaxation of the eligibility criteria for SR. The conventional restriction of this modality to patients with only three to four metastatic lesions has been relaxed to the inclusion of patients with many lesions, as long as an adequate residual hepatic volume is ensured. Unfortunately though, only 10%–15% of patients qualify for SR at the time of initial diagnosis. The remaining vast majority requires down-staging of the lesions prior to curative-intent SR, a process usually accomplished by the application of neo-adjuvant chemotherapy (Sabanathan et al., 2016).

Down-staging followed by curative-intent SR mandates a proactive engagement of multidisciplinary team represented by oncology, interventional radiology, hepatobiliary surgery, social services and pharmacy. The contribution of these disciplines is best convened by a tumor-board charged with the delineation and execution of an individualized multidisciplinary management plan. With SR as the ultimate goal, such a plan should outline a neo-adjuvant chemotherapeutic approach suited to the locally available resources, tumor biology and the extent of the primary and metastatic disease. As such, the components of chemotherapeutic regimens continue to evolve, reflecting the cumulative experience of clinical practitioners and the elaboration of novel molecular targets. An excellent recent review by Bresalier provides a comprehensive overview of the most commonly employed neo-adjuvant regimens (Bresalier, 2016). It is quite encouraging that the combination of chemotherapy and monoclonal antibodies can achieve success in as many as 80% of patients initially considered ineligible for SR (Prenen and Van Cutsem, 2012). Apart from neo-adjuvant chemotherapy, preoperative portal vein embolization (PVE) can be employed in selected cases to induce compensatory hypertrophy of the disease-free liver. This strategy can enable an extended hepatectomy for curative-intent SR. Interestingly, compensatory hypertrophy is typically rapid after PVE and most patients can be scheduled to undergo SR within 4–6 weeks after this procedure. This approach is usually considered when the estimated post-resection liver volume is less than 20% of the total liver volume. As a result of these innovative strategies, SR can be offered to all but those with absolute contraindications such as unresectable extrahepatic disease, liver involvement exceeding 70%, and those with coexisting liver failure (Poston et al., 2005). Patients who do not meet the resection criteria are evaluated for the most optimal alternative loco-regional therapies or palliative care.

Among a variety of loco-regional modalities, cryotherapy and radiofrequency ablation are the most widely utilized alternative approaches for patients with CRC metastases that are not amenable to SR (Abdalla et al., 2004). Whereas the mechanism of cryotherapy is rapid tissue freezing, radiofrequency ablation (RFA) employs an electrical current produced by radio waves to produce tumor ablation. RFA can be applied to down-stage the lesions or as a curative procedure during open surgery for small contralateral tumors in patients undergoing right or left hepatectomy (Abdalla et al., 2004; Minami and Kudo, 2013). A major disadvantage of all loco-regional ablative therapies remains as incomplete tumor demolition, especially for tumors larger than 4 cm or those in the vicinity of larger vessels. As such, it is preferable to avoid thermal ablation of lesions close to major hilar structures except as a part of a clinical trial conducted by highly experienced multidisciplinary teams. Another important caveat is the potential ablation of the surrounding normal parenchyma, which may compromise the remaining liver volume, especially following a combined resection and ablation procedure (Cirocchi et al., 2012).

In current clinical practice, SR is apparently the best option for mCRC in eligible candidates with marginal advantage over the use of targeted drugs. This situation represents an opportunity to understand the molecular mechanisms underlying the development of mCRC that can be exploited to improve drug efficacy. Our current understanding of the mechanism responsible for the spread of primary CRC is inadequate and requires further studies. However, the mechanisms underlying the initiation and progression of CRC have been studied more extensively and several models have been proposed. A critical analysis of these models could open up avenues that would aid in improving our understanding of mCRC with a focus on liver metastases (CLM).

3. Molecular models of initiation and progression of mCRC

Metastatic CRC signaling is a complex system that involves various molecular pathways. Three pathways have been shown to be significantly involved in mCRC; chromosomal instability, microsatellite instability and the CpG island methylator phenotype (Colussi et al.,

2013). Here, we review these pathways to assess their probable role and function in the context of liver metastasis.

3.1. Chromosomal instability

3.1.1. The wingless-type (WNT) signaling pathway

Chromosomal instability is the most common type of colorectal cancer signaling. This pathway involves different mitotic spindle checkpoint regulators and proteins that exert mutual influences on the stability of the mitotic chromosome (Orsetti et al., 2014). Early mutation of the adenomatous polyposis coli (APC) tumor suppressor gene is the initial significant mutation (Scapoli et al., 2011), which is involved in both Familial Adenomatous Polyposis (FAP) and sporadic chromosomal instability. Inactivation of the APC suppressor gene results in increased WNT signaling and failure to degrade β-catenin (Scapoli et al., 2011). Accumulation of β-catenin leads to its translocation into the nucleus and stimulates the T-cell factor (TCF) targets, with increased migration, differentiation, proliferation and adhesion of colorectal cells (Scapoli et al., 2011; Rouhi et al., 2008; Zhang et al., 2013; Karim et al., 2014; Burn et al., 2008).

High expression of β-catenin and TCF4 complexes are associated with upregulated expression of Yes-associated protein (YAP), which promotes metastasis in CRC. Low levels of YAP have a direct effect on reducing the levels of β-catenin, which might be used to improve therapeutic options in CRC although reports supporting this association are limited (Konsavage and Kyler, 2012). Integration of the WNT/β-catenin signaling pathway and the tumor microenvironment has been suggested to be related to the progression of CRC and metastasis. High expression of WNT3a and WNT5a genes is found less frequently in metastatic tumors than in primary CRC. It is very likely that the involvement of this pathway is significant in the initial phase of CRC progression. Expression of WNT3a is notably associated with MMP-9, which plays an important role in extracellular matrix dysregulation leading to invasion and metastasis (Lee et al., 2014). High frequencies of retinoblastoma gene (Rb) mutations are significantly associated with many epithelial cancers, including CRC with metastatic potential. Low levels of WNT/β-catenin signaling can be induced by Rb inactivation, which was found to result in the initiation of aggressive high grade CRC in a mouse model (Parisi et al., 2015). Studies have suggested that tumors expressing low levels of β-catenin in combination with p53 are associated with aggressive forms of cancer, with a high probability of metastasis (Pancione et al., 2010).

3.1.2. The RAS pathway

The WNT pathway involves early mutations in the CIN pathway that are followed by molecular events, which facilitate tumor progression. The KRAS gene mutation determines the adenoma-carcinoma transition. The KRAS gene is a proto-oncogene that encodes a GTPase protein (Burn et al., 2008) involved in the transduction and propagation of extracellular signals, such as mitogen-activated protein kinase (MAPK). A significant impact of KRAS mutations have a significant impact on cells by inducing a permanent activation that permits cells to evade apoptosis and acquire a growth advantage (Katkoori et al., 2009). Most KRAS mutations occur at codons 12 and 13 (Katkoori et al., 2009). Although mutations in codon 12 confer more oncogenic phenotypes, codon 13 mutations have greater involvement in the adenoma-carcinoma transition (Katkoori et al., 2009). High WNT activity is directly linked to increased MAPK signaling associated with KRAS mutations (Katkoori et al., 2009).

Activation of the TGF-β pathway results in a wide spectrum of physiological functions that increase cell migration and survival in mCRC. Activation of the RAS mutation has been suggested to be associated with CRC resistance to TGF-β-mediated growth inhibition. Furthermore, involvement of the TGF-β pathway in tumorigenesis and cell proliferation is indicated by activation of components of the non-Smad signaling pathways, such as extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), which can be inhibited by TGF-β receptor type I/II (TβRI/II) dual inhibitors (LY2109761). It has been reported that treatment using LY2109761 has a direct effect in decreasing the size of CLM and increasing survival in a mouse model (Zhang et al., 2009).

RAS-association domain family 1 isoform A (RASSF1A) is a member of the RAS-association domain family (RASSF). It binds to GTP-dependent proteins that activate the apoptosis pathway involved in the oncogenic function of RAS. In CLM, RASSF1A inactivation may lead to deregulation of the WNT/β-catenin signaling pathway, causing high levels of β-catenin. The increased levels of β-catenin promote the oncogenic function of this pathway (Schirosi et al., 2016). Sur8 is a RAS-RAF scaffold protein involved in cell motility and metastasis. Downstream signaling through the ERK pathway and the PI3K-AKT signaling pathway is modulated by Sur8, promoting cell growth and metastasis in CRC. It has been suggested that Sur8 represents a potential therapeutic target in mCRC (Kaduwal et al., 2015). Cancerous inhibitor of protein phosphatase 2 A (CIP2 A) is a protein in human cells encoded by the KIAA1524 gene. Expression of CIP2 A has an oncogenic effect on many tumors, including CRC, and is associated with tumorigenesis and cell migration. The significance of CIP2 A was highlighted by its association with the KRAS mutation in patients with CLM who underwent liver resection. Thus, indicating that CIP2 A may function as an important prognostic biomarker in this population (Chen et al., 2015). Phosphatase and tensin homolog (PTEN) loss in chromosome 10q causes dysregulation of the phosphoinositide-3-kinase (PI3K) signaling pathway by epigenetic silencing and promotion of methylation. Loss of PTEN expression is associated with CLM and it is correlated with RAS/BRAF mutations (Atreya et al., 2013).

3.1.3. The p53 signaling pathway

Mutation of the p53 gene (TP53), which is located on chromosome 17p, is one of the key steps in colorectal carcinogenesis. This gene promotes proliferative activity through the loss of cell cycle control (Firestein et al., 2008). The p53 gene controls BUBR1 gene transcription and expression and also regulates energy balance. CDK is involved in regulating stem cell aging, cellular senescence and energy status balance and p53 upregulates the CDK inhibitor via the AMPK pathway (Erler and Giaccia, 2006). The p53 gene also interacts with cyclooxygenase-2, with both playing a role in enhancing inflammation and cell proliferation in CRC (Rajaganeshan et al., 2009). There is a direct association between cyclooxygenase-2 positive tumors and an increased cancer-specific mortality, regardless of the p53 status (Rajaganeshan et al., 2009).

Low p53 expression is associated with increased neovascularization and metastasis. An association between p53 mutations and microvessel density have been reported, with an association between high microvessel density and p53 mutations in primary CRC and CLM. However, there is no notable association between p53 mutations and neoangiogenic vascular endothelial growth factor expression in CLM (Kern et al., 2002; Des Guetz et al., 2006).

Studies have shown that high levels of β-catenin can induce p53 accumulation, which enhances the transactivation function of p53 in inducing cell cycle arrest and promoting apoptosis. Conversely, low levels of β-catenin result in high rates of proteasomal degradation, yielding lower p53 expression via a negative feedback mechanism. In CLM, combinations of low β-catenin levels and high p53 levels were observed to lead to more aggressive cancer and poor prognosis. Thus, it is recommended that patients should be tested for expression of both p53 and β-catenin to identify the nature of the cancer and to determine the prognosis (Pancione et al., 2010).

Low BAX gene expression in CLM is reported to be unfavorable, resulting in reduced survival rates. In contrast, the prognosis is good in individuals with CLM who do not have dysregulated p53-to-BAX signaling. Therefore, testing of patients with CLM for the apoptosis signaling pathway rather than for p53 alone is recommended (Schelwies

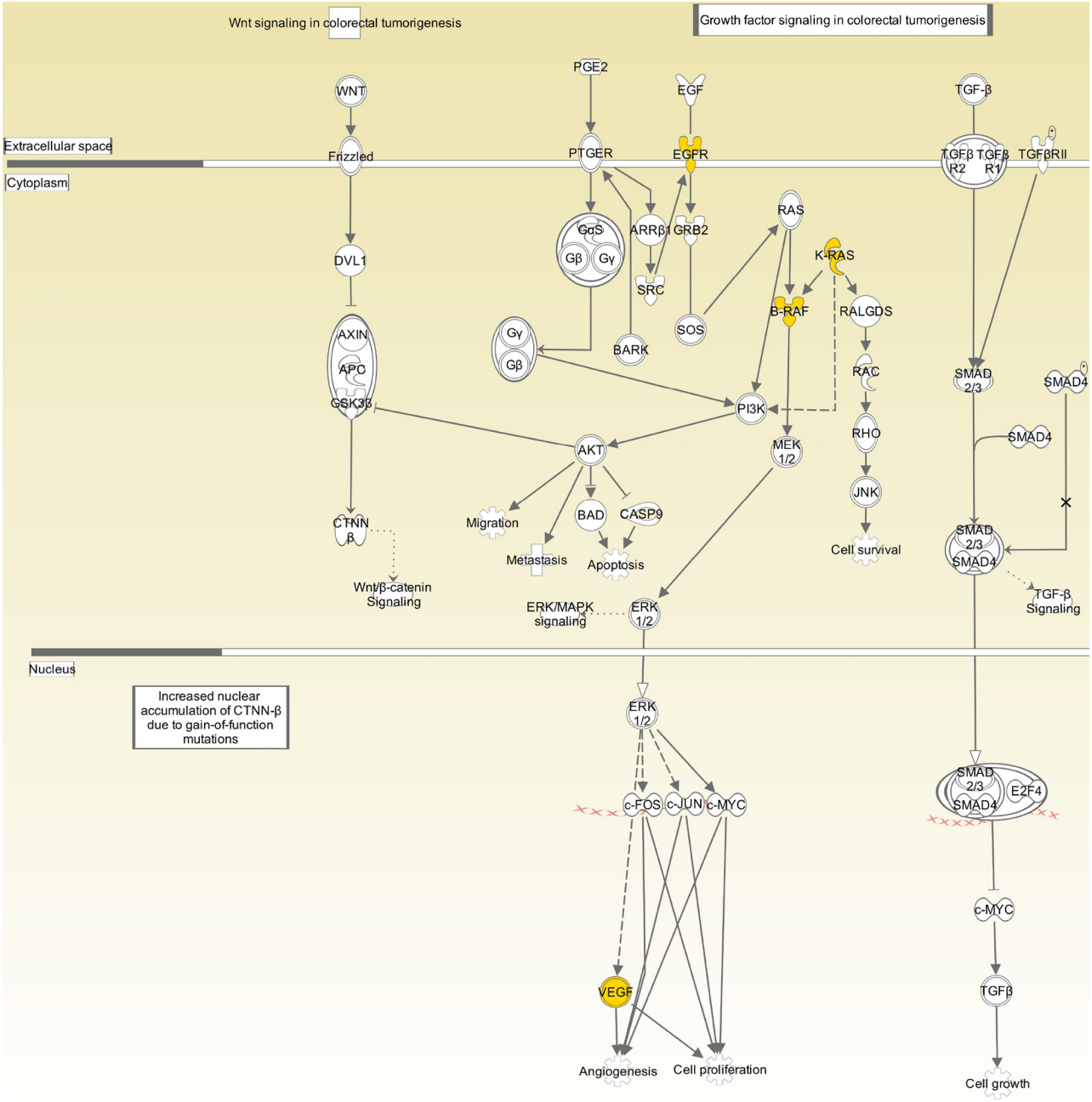

Fig. 1. Molecular pathways involved in colorectal cancer liver metastases. Most notable signaling pathways are Wnt/β-catenin, ERK/MAPK and TGF-β. Mutations in CTNNB gene is known to cause increase nuclear accumulation of the protein which could involve in liver metastasis. Molecules highlighted in yellow are candidate biomarkers (Colussi et al., 2013; Lièvre et al., 2006; Chen et al., 2015; Zhang et al., 2009) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

et al., 2002; Sturm et al., 1999).

The p53/MDM2/p14ARF pathway, which is one of the main signaling pathways involved in CRC, is involved in regulation of the apoptosis pathway. MDM2 has an oncogenic function and mediates p53 deregulation through autoregulation feedback. Overexpression and amplification of MDM2 have been associated with aggressive form of cancers in many malignancies, although studies have suggested otherwise in mCRC. MDM2 expression has been reported to be associated with a favorable prognosis in CLM (Kondo et al., 2008). The interplay of Wnt, Ras and p53 along with TGF-β pathway in relation to CLM has been depicted in Fig. 1.

3.2. The MSI pathway

Microsatellite instability (MSI) pathway is activated by the inactivity of the DNA mismatch repair (MMR) system. Disabling the DNA MMR leads to a 100% increase in the mutation rate in colorectal cells (Shibuya et al., 2011; Lipsyc et al., 2017). The MMR system is composed of multiple interacting proteins, including the human MutL homolog and functions as a proofing mechanism to increase the fidelity of DNA replications (Zhang et al., 2016). This process is made possible by identification and direct repair of mismatched nucleotides (Pérez-Cabornero et al., 2011). The involvement of MSI pathway in relation to colorectal cancer metastases has been illustrated in Fig. 2.

In CLM, high levels of Microsatellite instability (MSI-H) does not play any role in stratifying patients with hepatic resection and has no

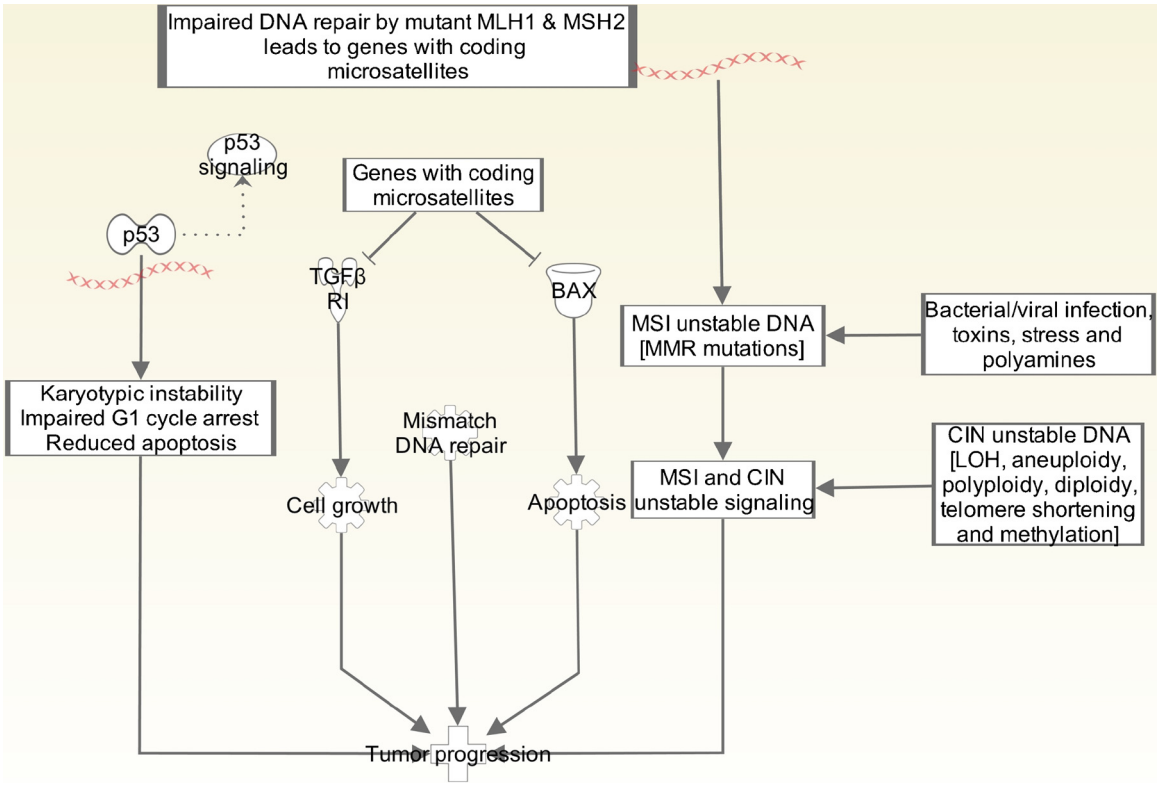

Fig. 2. Mismatch repair pathway is implicated in CRC metastasis. This includes Microsatellite instability (MSI), karyotypic instability and chromosomal instability (CIN) pathway. Due to non-functional DNA repair machinery p53, TGFB and BAX genes are affected resulting in altered cell growth and apoptosis (Wangefjord et al., 2013; Colussi et al., 2013; Sturm et al., 1999; Haddad et al., 2004; Liu et al., 2011; Gatalica et al., 2016).

prognostic value. Low frequency MSI was also reported in patients with mCRC, although it reflects neither the prognosis nor the severity of the disease. Evidence has shown that Microsatellite stability (MSS) in primary cancer results in a greater probability of developing liver metastasis-post-resection (Gatalica et al., 2016; Haddad et al., 2004). Loss of hMLH1 gene expression is representative of CRC with MSI and is associated with a lower incidence of metastasis. Expression of hMLH1 gene is representative of (MSS). Along with the activation of WNT/β-catenin signaling pathway and expression of CD133, MSS is significantly associated with aggressive CRC and liver metastatic potential (Neumann, 2016).

Activation of the PI3K/AKT pathway is mediated by the TGFβ receptor type 2 in MSI CRC and results in lower rates of apoptosis, while promoting cell proliferation. Evidence has shown that expression of the TGFβ receptor type 2 in MSI CRC is associated with higher cell survival and metastasis potential (Liu et al., 2011).

3.3. Gene mutations and copy number aberrations in mCRC

There are numerous distinctions between the genetic mutations in primary CRC and mCRC. Some studies have shown correlations of specific mutations with various roles in mCRC (Lipsyc and Yaeger, 2015), one of which, the KRAS mutation, has been extensively studied in the last few decades (Zhang et al., 2011). The KRAS exon 2 p.G12 V mutation has been commonly reported in mCRC and is associated with poor prognosis (Zhang et al., 2011). This is mainly due to its resistance to targeted therapy (anti-EGFR), which is the therapy of choice in mCRC (Amado et al., 2008). The exact mechanism underlying this resistance is unclear, although a few studies have indicated that the KRAS mutation deactivates the signaling response stimulated by EGFR, leading to decreased activation of the apoptosis pathway (Amado et al., 2008). Along with resistance to treatment and aggressiveness of the cancer, the KRAS mutation is also associated with higher recurrence rates in the lungs and liver ((69% and 31% of the total recurrences, respectively) (Kim et al., 2016a). The KRAS mutation has also been linked to higher incidence of recurrence following hepatic resection (Kim et al., 2016a).

Extensive studies have associated the BRAF V600E mutation located at chromosome 7q34 with aggressive CRC and mCRC. This mutation plays a significant role in disturbance in the MAPK pathway, which promotes cell proliferation and survival leading to poorer prognosis and high probability of metastases (Bedeir and Krasinskas, 2011; Sinicrope et al., 2015). At the molecular level, the BRAF mutation plays a role in early proliferation stages of CRC as well as in advanced CRC and cell migration, ultimately resulting in metastases (Martinelli et al., 2017). There is a strong association between the BRAF mutation and a distinct pattern of lymph node metastasis, with an overall increased frequency of CLM in individuals with lymph node invasion (Bedeir and Krasinskas, 2011; Sinicrope et al., 2015). However, the exact mechanism by which the BRAF mutation contributes to lymph node metastases remains to be fully elucidated.

The PIK3CA exon 20 mutation is associated with resistance to anti-EGFR therapies, such as cetuximab, and also serves as a therapeutic biomarker although it is less commonly used than KRAS mutation. The PIK3CA gene mutation leads to disruption in the production and activity of phosphatidylinositol 3-kinase (PI3K), which plays an important signaling role in controlling cell proliferation and migration (Roock et al., 2011). The PIK3CA mutation usually occurs in individuals exhibiting KRAS mutations and less commonly in those with the BRAF mutation, resulting in more aggressive proliferation and migration properties (Therkildsen et al., 2014). However, there is insufficient evidence to support an association between the presence of the PIK3CA mutation alone and reduced survival rates in mCRC. The mechanism by which the presence of PIK3CA mutation in combination with the KRAS or BRAF mutations in mCRC is associated with reduced survival rates and highly aggressive cancer is not yet clear.

In contrast to the extensively studied KRAS, BRAF and PIK3CA mutations, the FCGBP gene located at chromosome 19q13.2 has recently been reported to play a significant role in mCRC through its function in cell adhesion (Qi et al., 2016). The FCGBP gene encodes the IgGFc-binding protein, which has a structural role in mucosal protection and an anti-inflammatory role in the tissues. Further studies are required to explore the therapeutic potential and diagnostic value associated with FCGBP gene mutations (Qi et al., 2016).

Identification of genetic mutations in mCRC will provide a greater understanding of the predictors of disease progression and outcomes. KRAS, BRAF V600E, PIK3CA, TP53 and FCGBP gene mutations have been correlated with an increased tendency to progress to advanced CRC and mCRC. Unfortunately, reports describing thorough genetic profiling of mCRC patients are less common. This can be due to deficiencies in genetic testing and samples from metastatic sites as well as the absence of unified databases.

Many studies have been conducted to identify aberrations in CRC as well as mCRC. In the last few years, there has been pooling of information and data regarding different chromosomal events in both CRC and mCRC although reports of the differences in chromosomal abnormalities between CRC and those in mCRC are rare. Studies have shown strong correlations and distinctions between specific chromosomal events in certain genomic regions and the status of the tumor in CRC (Yamamoto et al., 2010). Many chromosomal abnormalities were found to be altered in CRC, but not in mCRC. In contrast, several chromosomal aberrations were reported in mCRC, but not in CRC. There are three main chromosomal regions in which abnormalities have been identified and associated with CLM (Yamamoto et al., 2010). Gains on 20p12-p13 and 20q11-q13 as well as losses on 6q14-q25 have been reported to be strongly associated with the presence of liver metastasis in patients with CRC (Yamamoto et al., 2010). Other studies have revealed chromosomal abnormalities associated with metastasis, but not exclusively in the liver, such as gains on 7p, 8p, and 13q as well as losses on 1p, 5q, 8p, 15q, 17p, 17q, and 18p (Yamamoto et al., 2010; González-González et al., 2014).

3.4. Differential gene expression in mCRC

Understanding gene expression is crucial to prediction of the course of the cancer and its severity (Raspe et al., 2012). Genetic alterations result in changes in gene expression. Many studies have introduced a list of metastasis-associated genes and differential expression of multiple genesin primary CRC and mCRC have been shown to correlate with different survival rates (Qi et al., 2016; Kleivi et al., 2007). The CEACAM7 mutation is implicated as a metastases-associated gene, with expression levels downregulated in CRC and upregulated in mCRC. This gene plays an important and complex role in the apoptosis pathway, cell polarity and also in invasion and adhesion characteristics of distant mCRC (Kleivi et al., 2007).

A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) form a family of multifunctional protease enzymes comprising 20 members that play roles in cell morphology, modeling, migration and angiogenesis (Filou et al., 2015; Alonso et al., 2015; Przemyslaw et al., 2013). ADAMTS1 is expressed at the highest level among the ADAMTS proteins (Filou et al., 2015; Kleivi et al., 2007). Down regulation of ADAMTS1, ADAMTS9, and ADAMTS19 have been reported to contribute to CLM (Alonso et al., 2015; Kleivi et al., 2007), while ADAMTS5 up regulation has been reported to be absent in the early stages of CRC and its expression is associated with an aggressive form of CRC (Filou et al., 2015). Gene expression changes can be regulated by miRNAs which are known to be of diagnostic and prognostic value in mCRC. Common gene expression changes associated with advanced CRC and CLM are listed in Table 1.

3.5. MicroRNAs in mCRC

Several miRNAs have been associated to play a role in suppressing liver metastases in CRC primarily by inhibiting cell growth and invasion (Chi and Zhou, 2016). MiR-214 plays a role in negative regulation of CLM and its expression is associated with better prognosis and prolonged survival rate (Chen et al., 2014a). MiR-483 has be identified as a strong endogenous suppressors of CLM, its expression results in hypoxic response by converting ATP and creatine to phosphocreatine (Chi and Zhou, 2016; Loo et al., 2015). Expression of miR-133a plays a role in targeting LIM and SH3 domain protein 1 (LASP1). It functions by suppressing tumor pathogenesis by inhibiting phosphorylation of the ERK/MEK signaling pathway (Wang et al., 2017).

MiRNA signatures are crucial in predicting the course of the cancer since they are helpful in identifying the primary lesion and its metastases (Esteller, 2011). Eighteen miRNAs have been shown to be associated with liver metastasis, 15 of which (miR-16, miR-21, miR-24, miR-26a, miR-26b, miR-29a, miR-31, miR-93, miR-103, miR-145, miR-155, miR-191, miR-194, miR-200c and miR-224) were upregulated and three (miR-328, miR-487b and miR-566) were downregulated. Differential gene expression correlates with different characteristics, prognoses and predictors during the course of CRC (Drusco et al., 2014; Valastyan et al., 2009; Hur et al., 2015; Orang, 2014; Hata et al., 2017; Amankwatia et al., 2015).

Upregulation of miR-21 is associated with poor survival (Tokarz and Blasiak, 2012) and plays a key role in the metastatic pathway by inducing cancer cell formation and invasion (Drusco et al., 2014). MiR-21 is overexpressed significantly in CLM as well as lymph node metastasis, indicating that miR-21 upregulation correlates with high metastatic potential (Drusco et al., 2014). Interestingly, miR-21 expression is also present in hepatocellular carcinoma, indicating the limited diagnostic significance of miR-21 in discriminating hepatocellular carcinoma from liver metastases (Karakatsanis et al., 2013). MiR-31 expression is upregulated in mCRC and associated with CLM (Drusco et al., 2014). Furthermore, miR-31 expression levels vary in different tumors; for example, upregulation is associated with poor prognosis in CRC, while downregulation tends to be associated with poor prognosis in breast cancer (Valastyan et al., 2009). MiR-93 is also reported to be overexpressed in CLM (Drusco et al., 2014). Similar to miR-21, both miR-31 and miR-93 have been reported to be overexpressed in mCRC and hepatocellular carcinomas and therefore, cannot be used as a diagnostic tool in discriminating these malignancies (Ohta et al., 2015; Li et al., 2009). In contrast, miR-103 is upregulated in CLM and can be used to distinguish between mCRC and hepatocellular carcinoma (Zheng et al., 2016). MiR-200c is significantly overexpressed in liver and lymph node metastases and is strongly associated with CRC progression and poor survival (Chen et al., 2014b). Along with miR-103, miR-200c can also be used to discriminate hepatocellular carcinoma from mCRC metastasis to the liver (Toiyama et al., 2014). Downregulation of miR-224 is associated with lymph node metastases; however, overexpression of miR-224 is significantly associated with CLM (Amankwatia et al., 2015). MiR-487b downregulation is associated with CLM and poor prognosis, but interestingly, better prognosis and higher survival rates are reported for individuals suffering from CLM with miR-487b overexpression (Hata et al., 2017). Further studies to provide more knowledge and data of novel molecular biomarkers and their associations with the course of the cancer are crucial to enhance the effectiveness of mCRC diagnosis and predicting the prognosis. More information about the associations of miRNAs with advanced metastatic colorectal cancer (but not restricted exclusively to liver metastases) can be seen in Table 2.

3.6. Mechanism of methylation in mCRC

DNA methylation based evidence can be used for diagnostic as well as prognostic purpose in CRC. methylation of DNA is a common

Table 1
Gene expressions changes in advanced colorectal cancer especially liver metastases.

Gene	Molecule type	Activity	Disease or function	Expression evidence
VEGFA	Growth factor	Increased	Metastatic colorectal cancer	Upregulation
TNFRSF11B	Transmembrane receptor	Increased	Metastatic colorectal cancer	Upregulation
TGFB2	Growth factor	Increased	Metastatic colorectal cancer	Upregulation
SMAD3	Transcription regulator	Increased	Metastatic colon cancer	Upregulation
SMAD2	Transcription regulator	Increased	Metastatic colon cancer	Upregulation
S100A4	Calcium binding protein	Decreased	Metastatic colorectal cancer	Downregulation
RPTOR	Cell growth regulation	Increased	Stage IV colorectal cancer	Upregulation
RICTOR	Cell growth regulation	Increased	Stage IV colorectal cancer	Upregulation
RAC1	Enzyme	Increased	Metastatic colorectal carcinoma	Upregulation
PTGS2	Enzyme	Increased	Metastatic colorectal cancer	Upregulation
PLS3	Actin-binding protein	Increased	Colorectal cancer with distant metastasis	Upregulation
PDGFA	Growth factor	Increased	Metastatic colorectal cancer	Upregulation
MTOR	Kinase	Increased	Stage IV colorectal cancer	Upregulation
FGF1	Growth factor	Increased	Metastatic colorectal cancer	Upregulation
CXCL12	Cytokine	Decreased	Metastatic colorectal cancer	Downregulation
CD44	Cell-surface glycoprotein	Increased	Metastatic colorectal carcinoma	Upregulation
CCL2	Cytokine	Increased	Metastatic colorectal cancer	Upregulation
AKR1C1/AKR1C2	Enzyme	Decreased	Metastatic colorectal cancer	Downregulation

epigenetic signaling tool that involves in transferring methyl group into C5 position of the cytosine by DNA methyltransferases (DNMT) forming 5-methylcytosine which is responsible for regulating gene expression. It does so by recruiting proteins involved in gene expressions and by inhibition of binding of transcription factors to DNA, causing cells to lock genes in the "off" position (Moore et al., 2013; Schübeler, 2015). DNA methylation of cytosine produces CpG dinucleotides which clusters to form CpG island methylator phenotype (CIMP) leading to transcriptional silencing of the associated genes that can be either hypomethylated and hypermethylated (Chen et al., 2017). Abnormal methylation of CpG islands in gene promoters and first exonic or intronic regions may induce the transcriptional silencing (Chen et al., 2017). Studies have linked (CIMP) to significantly poor outcome in terms of both low free survival and overall survival in CRC (Juo et al., 2014). Although the exact mechanism of DNA methylation and its relation to poor prognosis in CRC remain unexplained and it is not clear whether it is a primary pathological event or secondary phenomenon, methylation of multiple genes including MGMT, HLTF, MLH1, $p14^{ARF}$, p16, CDKN2 A, TIMP3, THBS1, CDH1, THBS1*, IGF2, HIC-1,* and *COX-2 are* described in the initiation and progression of CRC (Shen et al., 2007; Kim et al., 2006). DNA methylation seen in (CIMP) have two phenotype characteristics in terms of origin in the proximal colon and poor histological differentiation, however, there are still some contradictions in the literature in the association between (CIMP) and cancer specific molecular features of TP53 mutation, KRAS mutation, and MSI (Van Rijnsoever et al., 2002). Table 3 describespotential genetic and epigenetic biomarkers associated with mCRC.

Table 3
DNA Methylation biomarkers in mCRC.

Marker Gene	Material/ Tissue	Epigenetics	Pathways
SFRP2	Stool	Hypermethylation	Wnt signaling
SFRP1	Stool	Hypermethylation	Wnt signaling
MGMT	Stool	Hypermethylation	DNA mismatch repair
hMLH1	Serum	Hypermethylation	DNA mismatch repair
TFPI2	Stool	Hypermethylation	Serine proteinase inhibitor
MINT31	Serum	Hypermethylation	Promoter locus regulating calcium channels involved in p53 mutation
HPP1	Serum	Hypermethylation	Tumor suppressive epidermal growth factor (EGF)-like ligand
HLTF	Serum	Hypermethylation	DNA mismatch repair

Table 2
microRNAs associated with CLM.

MicroRNA	Expression evidence	Significance of the expression	Ref.
miR-16	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-21	Upregulation	Primary hepatic tumor and metastatic colorectal cancer	(Tokarz and Blasiak, 2012)
miR-24	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-26a	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-26b	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-29a	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-31	Upregulation	Differently expressed in various tumors; upregulation is associated with liver metastasis	(Valastyan et al., 2009)
miR-93	Upregulation	Primary hepatic tumor and metastatic colorectal cancer	(Ohta et al., 2015)
miR-103	Upregulation	Liver metastasis, but not of hepatic origin	(Zheng et al., 2016)
miR-145	Upregulation	Liver metastasis	(Toiyama et al., 2014)
miR-155	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-191	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-191	Upregulation	Liver metastasis	(Drusco et al., 2014)
miR-200c	Upregulation	Liver metastasis, but not of hepatic origin	(Chen et al., 2014b)
miR-224	Upregulation	Liver metastasis	(Amankwatia et al., 2015)
miR-328	Downregulation	Liver metastasis	(Drusco et al., 2014)
miR-487b	Downregulation	Liver metastasis, but upregulation associated with better outcome is also reported	(Hata et al. 2017)
miR-566	Downregulation	Liver metastasis	(Drusco et al., 2014)

Table 4
Biomarker genes associated with CLM.

Gene	Location	Family	Biomarker application(s)
B-RAF1	Cytoplasm	Kinase	Diagnosis, prognosis, response to therapy, unspecified application
CD44 (Indian blood group)	Plasma Membrane	Other	Diagnosis, disease progression, prognosis, unspecified application
EGFR	Plasma Membrane	Kinase	Diagnosis, disease progression, efficacy, prognosis, response to therapy, safety, unspecified application
ERBB2	Plasma Membrane	Kinase	Diagnosis, disease progression, efficacy, prognosis, safety
FGFR1	Plasma Membrane	Kinase	Diagnosis, prognosis, unspecified application
FGFR2	Plasma Membrane	Kinase	Diagnosis, response to therapy, unspecified application
FGFR3	Plasma Membrane	Kinase	Prognosis
FLT1	Plasma Membrane	Kinase	Diagnosis, disease progression, efficacy, prognosis, response to therapy, safety
FLT3	Plasma Membrane	Kinase	Efficacy, prognosis, response to therapy
FLT4	Plasma Membrane	Transmembrane receptor	Diagnosis, disease progression, efficacy, prognosis
KDR	Plasma Membrane	Kinase	Disease progression, efficacy, prognosis, response to therapy, safety
Kit	Plasma Membrane	Transmembrane receptor	Diagnosis, efficacy, prognosis, safety, unspecified application
MTHFR	Cytoplasm	Enzyme	Diagnosis, efficacy, response to therapy, safety
PDGFRA	Plasma Membrane	Kinase	Efficacy, prognosis, safety, unspecified application
PDGFRB	Plasma Membrane	Kinase	Prognosis, response to therapy, unspecified application
PGF	Extracellular Space	Growth factor	Diagnosis, disease progression, efficacy, prognosis
PLAU	Extracellular Space	Peptidase	Disease progression, efficacy, prognosis
	Cytoplasm	Group	Efficacy
RAF1	Cytoplasm	Kinase	Efficacy
RET	Plasma Membrane	Kinase	Efficacy, response to therapy
SERPINE1	Extracellular Space	Other	Diagnosis, disease progression, efficacy, prognosis, safety
TOP-1	Nucleus	Enzyme	Efficacy
TYMS	Nucleus	Enzyme	Diagnosis, disease progression, efficacy, prognosis, response to therapy
	Extracellular Space	Group	Diagnosis, disease progression, efficacy, prognosis, response to therapy, unspecified application
VEGF-A	Extracellular Space	Growth factor	Diagnosis, efficacy, prognosis, safety, unspecified application
VEGF-B	Extracellular Space	Growth factor	Efficacy, prognosis

4. Metastatic colorectal cancer therapy and biomarkers

4.1. mCRC biomarkers in clinical use

Biomarkers are statistically significant measurable indicators that represent valuable tools for evidence-based management of cancer patients (Newton et al., 2012; Gonzalez-Pons and Cruz-Correa, 2015; Henry and Hayes, 2012). To date, 33 biological molecules have been identified for which there is strong evidence of an association with CLM in humans. Of these, 26 molecules and molecular complexes are known to serve as biomarkers (Table 4). The BRAF mutation is now routinely monitored in a clinical setting for patients with the KRAS mutation. These biomarkers can be used for diagnostic and prognostic applications and have also been shown to be useful in assessing response to therapy, safety, efficacy and disease progression in CLM. Some of these biomarkers also represent potential therapeutic targets owing to their significant association with the disease. Many of these molecules (e.g. BRAF, VEGF, and EGFR) are located on the plasma membrane and extracellular space and are well-established drug targets. Other molecules located in the nucleus have also shown utility in predicting the response to therapy. For example, increased levels of thymidylate synthase show better response rates for 5- fluorouracil therapy (Karlberg et al., 2010).

4.1.1. The search for novel biomarkers of mCRC

There have been extensive studies and significant efforts in the past few decades investigating potential biomarkers of both CRC and mCRC. One of the most promising newly reported biomarkers in mCRC is a member of the vascular endothelial growth factor (VEGF) family, VEGF-B, which functions in maintaining angiogenesis (Yang et al., 2015). VEGF-B is associated with poor prognosis in primary tumors, but interestingly, studies have also shown that high VEGF-B levels in CLM actually improve the prognosis in individuals undergoing a hepatic resection (Stremitzer et al., 2016; Simiantonaki et al., 2007). Further large-scale studies are required to verify the role of VEGF-B in CLM.

Raf1 kinase inhibitor protein (RKIP) is reported to be a potential biomarker of mCRC. Loss of RKIP is correlated with tumor progression and poor prognosis in patients with CRC combined with distant metastasis (Minoo et al., 2007). As with many candidate biomarkers, RKIP is still not used in the clinical setting as most of the studies relevant to mCRC are retrospective in nature. Therefore, further studies are needed to provide significant evidence before RKIP can be introduced as a biomarker in the clinical setting (Zlobec, 2013).

Recently, metastasis-associated in colon cancer-1 gene (MACC1), which is located on chromosome 7p21.1, was reported to be a potential independent biomarker of mCRC (Stein et al., 2009). MACC1 has also been reported to be associated with poor survival and as a predictive marker of liver recurrence post-resection in mCRC (Isella et al., 2013). However, MACC1 is not predictive of the aggressiveness of CRC, which might be advantageous in clinical practice. The integration of MACC1 as a biomarker is not yet established as it has some restrictions (Zlobec, 2013).

Few studies have been performed to identify serum miRNAs in patients with CRC. Due to the correlation between high levels of miR-19a in serum and CRC progression, this molecule is implicated as a potential biomarker for determining the rate of disease progression and the aggressiveness of the tumor (Matsumura et al., 2015; Liu et al., 2017; Huang et al., 2015). MiR-19a upregulation is also associated with a higher recurrence rate (Matsumura et al., 2015). Furthermore, miR-19a has been detected in both early and advanced stages of CRC, giving it the potential to be an important prognostic biomarker in CRC (Matsumura et al., 2015).

Numerous biomarkers associated with different stages of CRC and metastases have been reported, although most are still not used in clinical practice due to insufficient evidence to support their relevance or significance in diagnosing, managing or determining the prognosis. There is a need for more studies in finding novel biomarkers to generate better evidence for determining the contribution of these molecules in the management of mCRC patients.

4.2. mCRC biomarkers from liquid biopsies

Liquid biopsies represent a fundamental tool in the management and work-up for any patient presenting with CRC or signs of advanced

Table 5
Common Gene Expression in Circulating Tumor Cells detected in CLM.

Symbol	Expression	Significance to the Expression	Ref
CDH1	Downregulated	Encoding E-Cadherin which has a role in EMT	(Kim et al., 2016b)
CDH17	Downregulated	Involved in cell adhesion	(Bartolomé et al., 2014)
CDX1	Downregulated	Increase β-catenin/TCF transcriptional activity	(Jones et al., 2015)
CEACAM5	Downregulated	Involved in cell adhesion	(Onstenk et al., 2016)
FABP1	Downregulated	Decreased expression of the fatty acid storage and glucose regulator	(Wood et al., 2016)
FCGBP	Downregulated	The significance of downregulation is not known	
IGFBP3	Downregulated	Interactions with the EMT-inducer transforming growth factor β (TGF-β)	(Onstenk et al., 2016)
IGFBP4	Downregulated	Interactions with the EMT-inducer TGF-β	(Onstenk et al., 2016)
MAPT	Downregulated	The significance of downregulation is not known	

CRC. This technique aids in predicting the genotype of the tumor and in monitoring the response to certain therapies.

Circulating tumor DNA (ctDNA) analysis has been introduced as a non-invasive method used to detect certain circulating mutations. Many hypotheses have been proposed for the mechanism by which tumor cells release nucleoid fragments into the circulation (Karachaliou et al., 2015). The main hypothesis is based on the release of fragments into the circulation after cell death, thereby increasing the levels of ctDNAs that can be detected by a blood test (Karachaliou et al., 2015). Analysis of RAS mutations in serum has been identified as a potential method for determining the tissue genotype and monitoring the response to treatment (Karachaliou et al., 2015; Schwaederle et al., 2016).

Circulating tumor cells (CTCs) are defined as cancerous cells that have migrated to the peripheral blood from either primary tumors or its metastases. The presence of CTCs is considered an undesirable finding because it reflects metastatic potential (Tsai et al., 2016). High levels of CTCs are usually detected after hepatic or primary tumor SR; therefore, some reports have recommended CTC isolation before surgery to prevent reduce the risk of misleading results (Kaifi et al., 2015; Weitz et al., 2000). Nevertheless, CTC analysis remains an important tool for the detection of early metastases of CRC (Tsai et al., 2016).

In CLM, nine genes are associated with circulating tumor cells (CTCs. Downregulation of CDH1, CDH17, CDX1, CEACAM5, FABP1, FCGBP, IGFBP3, IGFBP4 and MAPT were correlated to CLM (Onstenk et al., 2016). Common genes expression changes detected in CTCs during CLM are presented in Table 5.

5. Future of clinical practice in metastatic colorectal cancer

While clinical practices have improved allowing more accurate identification of patients who can benefit from surgical interventions as well as radiotherapy, the success of chemotherapeutic applications has been limited. This is largely because of the wide gaps that still exist in our understanding of molecular events that lead to liver metastases or metastases in general. Although we know the sequence of initiation and progression of CRC in most of the tumors, we are unable to define the threshold of molecular events that allow the cells to migrate and colonize other organs of the body. The “seed and soil theory” has not yet provided insights into what causes metastasis and we need to intensify our efforts to understand the molecular changes that cause the primary cells to dislodge and metastasize to preferred sites, like the liver. These efforts are important for the identification of biomarkers that facilitate earlier risk assessment of patients before it is too late for surgical intervention. The translational potential of these biomarkers will be enhanced by employing successful analysis of liquid biopsies. Efforts are underway to develop clinically actionable ways to analyze ctDNA for early detection. Another important and pertinent issue is the application of personalized medicine in metastatic patients. This requires a change in decision-making based on molecular evidence rather than empirical observations. The success of this approach necessitates the seamless integration of efforts among clinicians and scientists to establish a framework where decisions about the management of metastatic CRC patients can be made in a time and cost-effective manner.

6. Conclusion

CLM is associated with a poor survival rate and remains a difficult diagnosis (Zarour et al., 2017). Apart from the successful advances in surgical interventions, there has been little progress in increasing the survival rates for these patients. To date, the pathways known to be involved specifically with CLM have not been fully characterized. Some of the canonical pathways, such as WNT and RAS/Raf signaling are known to be associated with CLM. Better characterization of these pathways in the context of CLM will facilitate the development of customized treatment modalities. Biomarkers will play a crucial role in making timely and informed clinical decisions to carry out interventions with curative intent. Among the potential biomarkers, miRNAs hold the greatest promise for use in routine diagnostics. Liquid biopsies will change the landscape of early diagnosis and personalized medicine for cancer patients. Extensive research efforts are needed to elucidate the organ-specific molecular changes associated with distant metastases and provide information that can be used to develop better therapeutic strategies.

Conflict of interest

None

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