Copy number alterations in colorectal cancer

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Abstract: Genomic alterations have been recognized as key events in the initiation and progression of colorectal cancer (CRC), which are complex procedures comprising several sequential steps and orchestrated by networks of key molecular drivers. This review aim to summarize the current evidence, highlighting the importance of such changes in CRC. There exist multiple copy number alterations of chromosomes in CRC, and both protein- and non-protein coding genes (e.g., ROCK1, BRCA2, KLF5, PTK2, MYC, and miR-122) could be potentially affected, playing key roles in CRC biology, and providing novel directions for anti-CRC treatment. Copy number alterations could affect both tumor and metastasis genomes in CRC, and tumor and metastatic alterations could be very similar but some changes were more pronounced in the metastasizes. Further explorations concerning the functional aspects are warranted.

Keywords: Colorectal cancer, carcinogenesis, tumor progression, copy number alteration, next generation sequencing

Introduction

Copy number alteration (CNA) in cancer research

High-throughput next generation sequencing (NGS) methods have greatly facilitated genetic research in recent years [1]. Recently, data emanating from global whole genome sequencing projects suggest that loss of genome integrity especially CNAs contribute significantly to cancer progression [2]. CNAs, a form of structural variation, are changes of the genomic DNA resulting in the cell having an abnormal or, for some genes, a normal variation in the copy number of one or more sections of the DNA observed between two or more genomes [3]. CNAs, in contrast to single nucleotide polymorphisms (SNPs) which affect only one single nucleotide base, correspond to relatively large regions of the genome (usually > 1 kb) that have been deleted or duplicated on certain chromosomes [4].

An ideal CNA detection method should accurately quantify the copy number in all genomic segments and delineate their breakpoints across the whole genome [5]. Nowadays, several CNA-identifiable platforms with various accessible throughputs, read coverages, and resolutions are available: cytogenetic techniques including Fluorescence In Situ Hybridization (FISH) [6], NanoString’s digital detection technology [7], comparative genomic hybridization (CGH), array CGH [8], end-sequence profiling, virtual karyotyping with SNP arrays [9], and Next Generation Sequencing (NGS) [10], a technology simultaneously sequencing large numbers of short DNA strands from randomly fragmented copies of a genome, whose typical run could generate millions to billions of reads, which includes Whole Genome Sequencing (WGS) and Whole Exome Sequencing (WES), and which could be applied to quantitatively detect genomic mutations including point mutations, insertions, deletions (e.g. loss of heterozygosity [LOH]), duplications, inversions, and fusion products [11]. NGS offers accurate, highly sensitive, and of high resolution (1 kb), but the cost is the major drawback.

A CNA is one of the most important somatic genomic aberrations supporting tumorigenesis [12]. During carcinogenesis, tumor genomes
usually acquire somatic CNAs, namely, the amplification of oncogenes or deletion of tumor suppressor genes [13]. In screening for oncogenes, genomic regions with recurrent CNAs in tumor/metastasis genomes are believed to have a high possibility of containing malignant CNAs [14]. Up till now, various somatic CNA-affected tumor-associated genes have been identified across human cancers (solid, blood, and stromal tumors; for investigated cancer type details, refer to [12, 15]): amplification of ERBB2, EGFR, MYC, PIK3CA, IGF1R, FGFR1/2, KRAS, CDK4, CCND1, MDM2, MET and CDK6, and deletion of RB1, PTEN, CDKN2A/B, ARID1A, MAP2K4, NF1, SMAD4, BRCA1/2, MSH2/6, DCC and CDH1 [12, 15]. Different somatic mutation patterns could divide one cancer type into different sub-groups, and the prognoses and treatment responses of the discrepant subgroups might vary [16] (e.g., for HER2-positive breast cancer or metastatic gastric or gastroesophageal junction adenocarcinoma, Trastuzumab treatment significantly improved survival; for more examples, refer to [16]). Thus, CNA detection is an essential part of tumor genomic analysis, holding a great promise to improve cancer diagnostic and therapeutic strategies. This review highlights some novel tumor-related genes potentially affected by CNAs in CRC, with the possible mechanistic and functional importance in CRC discussed.

**Colorectal cancer (CRC)**

CRC is one of the most common and lethal malignancies worldwide, accounting for approximately 1.2 million new cases and 0.6 million deaths per year [17, 18]. Surgery is the major treatment modality [19]. Progressive tumors that invade within the colorectal wall (TNM stages I and II) are curable by surgical excision, but if unmanaged, they spread to regional lymph nodes (stage III) and then metastasize to distant sites (stage IV) [20]. Over 70% of stage III diseases are curable by surgery together with adjuvant chemoradiotherapy. Although recent therapeutic advances have improved survival, stage IV tumors are hardly curable [21, 22]. Although neoadjuvant chemoradiotherapy achieves low local recurrence rates, it delays administration of optimal chemotherapy, but nonetheless offers equally similar outcomes in selected patient groups [23].

The evolution of colorectal tissue from normal epithelium through adenoma to cancer and finally metastasis is characterized by accumulated abnormalities of particular genes [24, 25]. The processes involved in metastatic dissemination include: degradation of the extracellular matrix (ECM) components, accelerated cell motility and epithelial-mesenchymal transition (EMT), local invasion, angiogenesis, vascular and/or lymph vessel dissemination, immune evasion, distant colonization, and survival and growth in the novel microenvironment, with various key molecular regulators involved in each step [26, 27]. Investigating novel molecular mechanisms modulating CRC progression and discovering potential metastasis regulators will help to further elucidate CRC biology, and may provide new biomarkers for early CRC detection and potentially efficient targets for preventive and curative anti-CRC intervention approaches.

**CRC metastasis**

Metastasis, the process malignant cells disseminate from the primary tumor to colonize at distant sites, is the leading cause of cancer deaths worldwide, and the liver is the most common CRC metastatic site [19, 28]. The process of metastasis involves a complex cascade of events that culminate in the metastatic colonization of distant sites. Various genetic and epigenetic events causing loss of function of tumor suppressor genes and gain of function of oncogenes make tumor cell competitive in the metastasis process. Five models have been proposed to explain the metastasis process: the clonal selection model, the parallel evolution model, the dynamic heterogeneity model, the clonal dominance modal, and the stem cell model [29-31]. The CRC metastasis might occur at an early stage, and the microenvironment, cancer stem cell, and immune cell greatly modulate tumor metastasis [31, 32]. Microarray analyses also revealed that mRNA expression and DNA copy number patterns of metastasis were highly similar to those of the primary tumor [33]. Several sequential and sometimes overlapping molecular events have been implicated in CRC metastatic process and data emanating from global whole genome sequencing projects indicate that loss of genome integrity also contributes significantly to cancer progression [34]. Various genes have been reported to be involved in various steps of the CRC metastasis cascade: proteolysis, MMP-7 (matrylisin), MMP-9 (gelatinases),...
MMP-1, -8, -13 (collagenases), MMP-3 (stromelysin-1), TIMP-1, and uPAR; altered adhesion, Integrins, Cadherins, CD44, and CEA; angiogenesis, VEGF and PD-ECGF; cell survival, growth and evasion from the immune system, TRAIL-R, CXCR4, Drg-1, and c-Met. The expression of the CRC metastasis-associated genes could be modified by various mechanisms, including chromosomal instability, micro-satellite instability, and epigenetic modulation [26]. Our understanding of molecular events involved in CRC metastasis is still limited. CRC metastasis might emerge in the context of a specific tumor genetic background, further affecting control of growth and proliferation. The metastatic CRC stem cell has also been proposed to be integral to metastasis progression [35]. The investigation of such particular genetic alterations that would contribute to identifying patients at risk of metastasis could contribute greatly to the development of new strategies for CRC diagnosis and treatment.

**CNA in CRC metastasis**

Most genetic investigations in CRC have so far focused on those abnormalities that are acquired by primary tumors, whereas not many studies have compared the genetic aberrations of primary versus paired metastatic tumors. The metastasis process is related to the accumulation of genetic alterations in cells originating from primary tumors. Advances in DNA sequencing technology have made it possible to sequence the entire genome of cancers, and CRC provided the first example of its applicability [36]. Unexpectedly, the evaluation of the full-genome sequencing results from primary CRCs and distant metastases in the same patient showed few novel mutations in the metastases, suggesting that new mutations are not required to enable a cancer cell to metastasize [37, 38]. Sequence analysis of coding regions in primary and metastatic cancer genomes also suggest that only a few mutations are required to transform local malignant cells in CRC into invasive cells with metastatic capability [37]. Necessary genetic aberrations required for metastasis could occur in the primary tumor before the metastatic dissemination. Genomic instability can drive CRC development by facilitating the acquisition of multiple cancer-associated mutations [39]. The most common type is chromosomal instability, including numerous alterations in chromosomal copy number and structure [40]. It is an efficient factor causing the loss of a wild-type copy of tumor-suppressor genes, especially APC, P53, and SMAD family member 4 (SMAD4) [39]. In contrast to some other cancer types, CRC does not commonly have amplifications of gene copy number or gene rearrangements [41].

In recent years, multiple recurrent cytogenetic chromosomal abnormalities identified in primary tumors have been associated with CRC liver metastasis, including numerical gains of chromosomes 1q, 2p, 3q, 5p, 6q, 7, 8q, 11p, 13q, 20q, etc. and losses of chromosomes 1p, 3p, 4, 5q, 8p, 10q, 14q, 15q, 17p, 18q, 21, 22q, Xp, etc. [42, 43]. A study on genomic discrepancies discovered in primary CRC versus paired cerebral metastasis have depicted genetic alterations including gains of 8q, 12p, 12q, 20p, and loss of 5q in brain metastasis [44], which is somewhat different from the observation in liver metastasis, and the difference could be possibly be explained by the ‘seed and soil’ theory [45].

Del(18q) has long been observed in CRC using a broad panel of techniques ranging from conventional cytogenetics and FISH to CGH, array CGH, Multiplex Ligation-dependent Probe Amplification (MLPA), and SNP arrays, and the 18q21 cytoband has been reported to be the most frequently changed [46, 47]. This region comprises the DCC and SMAD genes, which are typically associated with advanced CRC [43, 48]. ROCK1 and mir-122, 2 vital tumor/metastasis-associated genes, are also located in the region. Loss of 18q12-qter is an independent prognostic marker especially for stage III/IV tumors [49]. Within this area, phosphatidylinositol-3-kinase, catalytic subunit type 3 (PIK3C3) is recurrently associated with the metastatic process. Using CGH, an association between del(18q23) and both lymphatic and liver metastases has been established [50]. With SNP arrays, loss of the 18q22-18q23 was found in the great majority of the metastasis [51]. Regarding chromosome 13q, which contains vital cancer-associated genes like BRCA2 and KLF5, amplified regions have been established to be associated with oncogenesis and metastasis [42, 43]. An association between amplification of the chromosomal regions 13q31.3, 13q34, and 20q13.33 containing genes MIRHG1, COL4A1, COL4A2, and CDH4 and
tumor metastasis has been reported [51]. Based on CGH and FISH, gain of 8q and loss of 8p have been detected in CRC, and appeared more frequent in metastasis than in primary CRC [42, 52, 53]. The well-known oncogene MYC, located on 8q24.12-8q24.13, and was reported to be amplified and over-expressed in both primary and metastatic tumors, and the tyrosine phosphatase PRL3/PTP4A3 on 8q24.3 was shown to be over-expressed in CRC metastasis [54, 55]. Based on cell lines, PTK2, SLA, RECQL4, TPD52, and EIF3S6 were reported to be possibly linked to metastasis [53]. Other genes including ANGPT2 on chromosome 8p have also been reported to be metastasis-related [51]. The 20q gain in CRC has also been reported to be linked with CRC metastasis [42, 56]. Amplification of 20q13.2 (especially the ZNF217 gene) was revealed correlated with the CRC metastatic potential and progression [57]. The ID1 gene on 20q is also metastasis-associated [51].

CNA-affected genes in CRC

A CNA could affect multiple protein-coding and none-protein-coding genes which are contained in the same fragment simultaneously, causing the subsequent functional changes. The location of a gene within the affected region might determine its copy number, and a copy number change often affects multiple genes in a similar pattern. The copy number alterations might affect both tumor and metastasis genomes in CRC. CNA study could help to uncover novel genes with key pro-oncogenic and/or pro-metastasis functions. Hopefully, some of the genes and their encoding proteins will be established as diagnostic and/or prognostic markers and/or therapeutic targets. Herein 6 potentially affected genes in CRC are discussed.

Rho-associated, coiled-coil containing protein kinase 1 (ROCK1)

ROCK1 plays an oncogenic role in cancers [58, 59]. ROCK1 encodes a protein serine/threonine kinase that is activated when bound to the GTP-bound form of the small GTPase Rho, which regulates formation of focal adhesions and stress fibers of fibroblasts, as well as adhesion and aggregation of platelets and lymphocytes by shuttling between the inactive GDP-bound form and the active GTP-bound form. Rho is also essential in cytokinesis and plays a role in transcriptional activation by serum response factor. ROCK1, a downstream effector of Rho, phosphorylates and activates LIM kinase, which in turn, phosphorylates cofilin, inhibiting its actin-depolymerizing activity [60]. Overexpression of ROCK1 and the G protein RhoA have been implicated in cancer progression. RhoA-bound ROCK1 phosphorylates myosin light chain (MLC), a necessity for acto-mysin contraction. RhoA also activates the focal adhesion kinase (FAK) signaling [58, 60]. The ROCK1 protein has been reported to be significantly over-expressed in CRC, compared to the adjacent normal mucosa, and to be negatively correlated with patients’ 5-year survival through Kaplan-Meier survival analysis. It has a better efficacy in predicting patient outcomes compared to tumor staging, and may provide a less invasive method of assessing patient prognosis [61].

Breast cancer 2, early onset (BRCA2)

BRCA2 is considered a tumor suppressor gene, and is involved in maintenance of genome stability, particularly in the homology-based recombination approach for repair of DNA double-strand break [62]. Tumors with BRCA2 mutations usually demonstrate loss of heterozygosity of the wild-type allele. Mutations in BRCA2 predispose humans to malignancies, especially breast and ovarian cancers [59, 63]. However, there exists controversy concerning the risk of CRC conferred by germline mutations in BRCA2 [64]. Some studies reported that germline BRCA2 mutation was associated with an increased CRC risk [65], and that CRCs may be part of the tumor spectrum associated with BRCA2biallelic mutations [66]. BRCA2 expression is enhanced in the apical pole of malignant epithelial cells and in nuclear foci of CRC compared to the corresponding normal tissues [67]. BRCA2 is more highly expressed in tumors when compared to normal tissues [68].

Krüppel-like factor 5, intestinal (KLF5)

KLF5 encodes a member of the Krüppel-like factor subfamily of zinc finger proteins, and is required to maintain embryonic stem cells in an undifferentiated state. The KLF5 protein is a mitogen- and stress-inducible transcriptional activator primarily expressed in the rapidly dividing intestinal crypt epithelial cells, and plays a crucial role in intestinal development
and homeostasis [69, 70]. It binds directly to a specific recognition motif in the promoters of target genes including various cyclins, acting as downstream of various signaling pathways especially the mitogen-activated protein kinase (MAPK) signaling, and regulating proliferation, and is regulated by post-translational modification. Loss of KLF5 from the colonic epithelium induces a regenerative response [71]. The gene expression may differ in discrepant cancers and in cardiovascular disease [72]. In CRC, KLF5 promotes proliferation of human CRC cells and intestinal tumor formation in mice. It plays a crucial role in the activation of β-catenin, which exerts key functions during cancer cell epithelial-mesenchymal transition (EMT), promoting tumor invasion and metastasis [73]. KLF5 mediates the transforming effects of oncogenic H-Ras, and is important in regulating CRC genesis, thus KLF5 inhibitors are of potential interest in anti-cancer therapy [74, 75].

Protein tyrosine kinase 2 (PTK2)

PTK2 encodes a cytoplasmic protein tyrosine kinase which is found concentrated in the focal adhesions forming between cells. The encoded PTK2/focal adhesion kinase (FAK) protein is a member of the FAK subfamily of protein tyrosine kinases. Activation of PTK2 might be an important early step in cell growth via various intracellular signaling transduction pathways responsive to cell interactions with the extracellular matrix. In CRC, FAK promotes malignant survival, proliferation, invasion, and migration after phosphorylation, and is a promising anti-tumor target [76]. There is a gradual increase in the expression of FAK with progression from normal epithelium to carcinoma to liver metastasis [77]. FAK expression correlated significantly with tumor stage, and could serve as an independent predictor of survival in CRC [78].

V-myc avian myelocytomatosis viral oncogene homolog (MYC)

The MYC protein is a multifunctional, nuclear phosphoprotein which regulates cell cycle, apoptosis, and cell transformation as a master transcription factor. Mutations, overexpression, rearrangement and translocation of MYC, a classic and well-characterized oncogene, have been associated with a variety of tumors, especially hematopoietic tumors [79]. Deregulated expression of MYC is a stimulator of CRC genesis and progression, and inhibiting MYC may have significant therapeutic significance [80]. In CRC, MYC was associated with tumor stage, and interestingly, CRC with overexpressed MYC demonstrated controversial survival [81, 82]. MYCCNA has been previously investigated in the colorectal tissue, especially in the carcinogenesis exploration. Compared to normal, MYC was up-regulated in adenoma, greatly promoting cell proliferation [83]. There is no significant difference in copy number between the normal, tumor, and metastasis tissues according to a report using FISH [84]. Using DNA flow cytometry and immune-staining, Zalata et al. [85] reported that primary malignancies were significantly more diffusely positive for MYC than the metastases. Using FISH, Obara et al. [86] showed that stage III and IV CRC had significantly higher copy numbers of MYC than the earlier stage diseases.

MicroRNA 122 (miR-122)

Hsa-miR-122, a bona fide tumor suppressor, might present cancer type-based heterogeneity. It is down-regulated in hepatocellular cancer (HCC), and its down-regulation promotes HCC progression [87, 88]. In breast cancer, malignancy-derived extracellular miR-122 is able to reprogram systemic energy metabolism to facilitate tumor progression and metastasis [89], miR-122 is also associated with CRC progression [90, 91]. The study by Iino et al. [91] reported that the most abundant miRNA in liver metastases compared to primary tumors was miR-122, suggesting that miR-122 overexpression in the primary tumor plays important roles in the development of CRC liver metastasis, with a significant difference in the expression between tumor and metastases samples was observed. However, the RNA from Iino and colleagues was from formalin-fixed paraffin-embedded CRC specimens, which might be accompanied with the problems regarding RNA preservation, thus influencing the accuracy of the results. miR-122 might also present a strategy in the battle of 5-Fluorouracil resistance in CRC [90]. Up until now, only PKM2 and the cationic amino acid transporter 1 (CAT1) have been established as targets of miR-122 in CRC [90, 91]. More targets are to be explored.
Further functional and mechanistic experiments are warranted to reveal the molecular roles in CRC progression. The question remains whether all the CNA-affected genes are functionally important for tumor progression.

**Perspective**

Since metastatic CRC is highly lethal, it is of great clinical interest to predict the metastatic potential of the primary tumor. Genomic profiling might be helpful in identifying a subgroup of patients with high risk of developing liver metastasis. This is particularly pertinent in this era of personalized targeted anti-cancer therapy where it is highly important to recognize the different characteristics of primary and metastatic tumors. Current clinical practice usually analyzes primary tumor material to determine molecular targets in the treatment of patients, which is actually oriented towards tackling the metastases [38]. Since the genomic profiles in the primary and metastatic tumors are highly similar, this approach is partly justified, nonetheless there are still metastasis-enriched and metastatic-specific molecular changes that could be of great potential significance. Moreover, it is also important to identify genomic alterations associated with prognosis. The presence of multiple structural and/or numerical chromosome alterations precludes the investigation of chromosomal instability subtypes.

A complicated transcriptional/post-transcriptional regulatory mechanism plays a significant role in determining the expression level of genes. It is important to mention that the sample source and molecular methods used in experiments can sometimes affect the reported results. It is noteworthy that since a primary CRC can be relatively large and only a small section might be taken for CNA analysis, heterogeneity could be reflected in the measurements and explains part of the potential differences. For the CNA validation experiments, the NGS- and RT-PCR-based approach is highly sensitive and specific, and in comparison to other methods used for analyzing CNAs, one of the most accurate in investigating the copy number of genes.

**Conclusion**

There exist multiple copy number alterations of chromosomes in CRC, and both protein- and non-protein coding genes could be potentially affected, playing key roles in CRC biology and anti-CRC treatment.

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**Disclosure of conflict of interest**

None.

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