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Review Article

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 metastasis. 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 oncotargets, genomic regions with recurrent CNAs in tumor/metastasis genomes are believed to have a high possibility of containing malignant genes [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-2*, *-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-myosin 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 through 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]. *MYC*CNA 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-Fluormyacil 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

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References

[1] Alkan C, Kidd JM, Marques-Bonet T, Aksay G, Antonacci F, Hormozdiari F, Kitzman JO, Baker C, Malig M, Mutlu O, Sahinalp SC, Gibbs RA and Eichler EE. Personalized copy number and segmental duplication maps using next-generation sequencing. Nat Genet 2009; 41: 1061-1067.

[2] Yang R, Chen B, Pfutze K, Buch S, Steinke V, Holinski-Feder E, Stocker S, von Schonfels W, Becker T, Schackert HK, Royer-Pokora B, Kloor M, Schmiegel WH, Buttner R, Engel C, Lascorz Puertolas J, Forsti A, Kunkel N, Bugert P, Schreiber S, Krawczak M, Schafmayer C, Propping P, Hampe J, Hemminki K and Burwinkel B. Genome-wide analysis associates familial colorectal cancer with increases in copy number variations and a rare structural variation at 12p12.3. Carcinogenesis 2014; 35: 315-323.

[3] Wain LV, Armour JA and Tobin MD. Genomic copy number variation, human health, and disease. Lancet 2009; 374: 340-350.

[4] McCarroll SA and Altshuler DM. Copy-number variation and association studies of human disease. Nat Genet 2007; 39: S37-42.

[5] Liu B, Morrison CD, Johnson CS, Trump DL, Qin M, Conroy JC, Wang J and Liu S. Computational methods for detecting copy number variations in cancer genome using next generation se-

quencing: principles and challenges. Oncotarget 2013; 4: 1868-1881.
[6] Speicher MR and Carter NP. The new cytogenetics: blurring the boundaries with molecular biology. Nat Rev Genet 2005; 6: 782-792.
[7] Northcott PA, Shih DJ, Peacock J, Garzia L, Morrissy AS, Zichner T, Stutz AM, Korshunov A, Reimand J, Schumacher SE, Beroukhim R, Ellison DW, Marshall CR, Lionel AC, Mack S, Dubuc A, Yao Y, Ramaswamy V, Luu B, Rolider A, Cavalli FM, Wang X, Remke M, Wu X, Chiu RY, Chu A, Chuah E, Corbett RD, Hoad GR, Jackman SD, Li Y, Lo A, Mungall KL, Nip KM, Qian JQ, Raymond AG, Thiessen NT, Varhol RJ, Birol I, Moore RA, Mungall AJ, Holt R, Kawauchi D, Roussel MF, Kool M, Jones DT, Witt H, Fernandez LA, Kenney AM, Wechsler-Reya RJ, Dirks P, Aviv T, Grajkowska WA, Perek-Polnik M, Haberler CC, Delattre O, Reynaud SS, Doz FF, Pernet-Fattet SS, Cho BK, Kim SK, Wang KC, Scheurlen W, Eberhart CG, Fevre-Montange M, Jouvet A, Pollack IF, Fan X, Muraszko KM, Gillespie GY, Di Rocco C, Massimi L, Michiels EM, Kloosterhof NK, French PJ, Kros JM, Olson JM, Ellenbogen RG, Zitterbart K, Kren L, Thompson RC, Cooper MK, Lach B, McLendon RE, Bigner DD, Fontebasso A, Albrecht S, Jabado N, Lindsey JC, Bailey S, Gupta N, Weiss WA, Bognar L, Klekner A, Van Meter TE, Kumabe T, Tominaga T, Elbabaa SK, Leonard JR, Rubin JB, Liau LM, Van Meir EG, Fouladi M, Nakamura H, Cinalli G, Garami M, Hauser P, Saad AG, Iolascon A, Jung S, Carlotti CG, Vibhakar R, Ra YS, Robinson S, Zollo M, Faria CC, Chan JA, Levy ML, Sorensen PH, Meyerson M, Pomeroy SL, Cho YJ, Bader GD, Tabori U, Hawkins CE, Bouffet E, Scherer SW, Rutka JT, Malkin D, Clifford SC, Jones SJ, Korbel JO, Pfister SM, Marra MA and Taylor MD. Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature 2012; 488: 49-56.
[8] Kallioniemi A, Kallioniemi OP, Sudar D, Rutovitz D, Gray JW, Waldman F and Pinkel D. Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. Science 1992; 258: 818-821.
[9] Alkan C, Coe BP and Eichler EE. Genome structural variation discovery and genotyping. Nat Rev Genet 2011; 12: 363-376.
[10] Metzker ML. Sequencing technologies-the next generation. Nat Rev Genet 2010; 11: 31-46.
[11] Medvedev P, Stanciu M and Brudno M. Computational methods for discovering structural variation with next-generation sequencing. Nat Methods 2009; 6: S13-20.
[12] Beroukhim R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, Barretina J, Boehm JS, Dobson J, Urashima M, Mc Henry KT, Pinchback RM, Ligon AH, Cho YJ, Haery L, Greulich H, Reich M, Winckler W, Lawrence MS, Weir BA, Tanaka KE, Chiang DY, Bass AJ, Loo A, Hoffman C, Prensner J, Liefeld T, Gao Q, Yecies D, Signoretti S, Maher E, Kaye FJ, Sasaki H, Tepper JE, Fletcher JA, Tabernero J, Baselga J, Tsao MS, Demichelis F, Rubin MA, Janne PA, Daly MJ, Nucera C, Levine RL, Ebert BL, Gabriel S, Rustgi AK, Antonescu CR, Ladanyi M, Letai A, Garraway LA, Loda M, Beer DG, True LD, Okamoto A, Pomeroy SL, Singer S, Golub TR, Lander ES, Getz G, Sellers WR and Meyerson M. The landscape of somatic copy-number alteration across human cancers. Nature 2010; 463: 899-905.
[13] Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, Speed D, Lynch AG, Samarajiwa S, Yuan Y, Graf S, Ha G, Haffari G, Bashashati A, Russell R, McKinney S, Group M, Langerod A, Green A, Provenzano E, Wishart G, Pinder S, Watson P, Markowetz F, Murphy L, Ellis I, Purushotham A, Borresen-Dale AL, Brenton JD, Tavare S, Caldas C and Aparicio S. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 2012; 486: 346-352.
[14] Beroukhim R, Getz G, Nghiemphu L, Barretina J, Hsueh T, Linhart D, Vivanco I, Lee JC, Huang JH, Alexander S, Du J, Kau T, Thomas RK, Shah K, Soto H, Perner S, Prensner J, Debiasi RM, Demichelis F, Hatton C, Rubin MA, Garraway LA, Nelson SF, Liau L, Mischel PS, Cloughesy TF, Meyerson M, Golub TA, Lander ES, Mellinghoff IK and Sellers WR. Assessing the significance of chromosomal aberrations in cancer: methodology and application to glioma. Proc Natl Acad Sci U S A 2007; 104: 20007-20012.
[15] Santarius T, Shipley J, Brewer D, Stratton MR and Cooper CS. A census of amplified and overexpressed human cancer genes. Nat Rev Cancer 2010; 10: 59-64.
[16] Dancey JE, Bedard PL, Onetto N and Hudson TJ. The genetic basis for cancer treatment decisions. Cell 2012; 148: 409-420.
[17] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
[18] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
[19] Huang L, Li TJ, Zhang JW, Liu S, Fu BS and Liu W. Neoadjuvant chemotherapy followed by surgery versus surgery alone for colorectal cancer: meta-analysis of randomized controlled trials. Medicine (Baltimore) 2014; 93: e231.
[20] Markowitz SD, Dawson DM, Willis J and Willson JK. Focus on colon cancer. Cancer Cell 2002; 1: 233-236.

[21] Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kroning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schuller J, Seitz JF, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J and Scheithauer W. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005; 352: 2696-2704.

[22] Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, Bardet E, Beny A, Ollier JC, Bolla M, Marchal D, Van Laethem JL, Klein V, Giralt J, Clavere P, Glanzmann C, Cellier P, Collette L; Group ERO. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014; 15: 184-190.

[23] Schrag D, Weiser MR, Goodman KA, Gonen M, Hollywood E, Cercek A, Reidy-Lagunes DL, Gollub MJ, Shia J, Guillem JG, Temple LK, Paty PB and Saltz LB. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014; 32: 513-518.

[24] Davies RJ, Miller R and Coleman N. Colorectal cancer screening: prospects for molecular stool analysis. Nat Rev Cancer 2005; 5: 199-209.

[25] Fearon ER and Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990; 61: 759-767.

[26] Takayama T, Miyanishi K, Hayashi T, Sato Y and Niitsu Y. Colorectal cancer: genetics of development and metastasis. J Gastroenterol 2006; 41: 185-192.

[27] Huang L, Xu AM and Liu W. Transglutaminase 2 in cancer. Am J Cancer Res 2015; 5: 2756-2776.

[28] Valastyan S and Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell 2011; 147: 275-292.

[29] Sleeman JP, Nazarenko I and Thiele W. Do all roads lead to Rome? Routes to metastasis development. Int J Cancer 2011; 128: 2511-2526.

[30] Klein CA. Parallel progression of primary tumours and metastases. Nat Rev Cancer 2009; 9: 302-312.

[31] Bernards R and Weinberg RA. A progression puzzle. Nature 2002; 418: 823.

[32] Sleeman JP, Christofori G, Fodde R, Collard JG, Berx G, Decraene C and Ruegg C. Concepts of metastasis in flux: the stromal progression model. Semin Cancer Biol 2012; 22: 174-186.

[33] Vakiani E, Janakiraman M, Shen R, Sinha R, Zeng Z, Shia J, Cercek A, Kemeny N, D'Angelica M, Viale A, Heguy A, Paty P, Chan TA, Saltz LB, Weiser M and Solit DB. Comparative genomic analysis of primary versus metastatic colorectal carcinomas. J Clin Oncol 2012; 30: 2956-2962.

[34] De Roock W, De Vriendt V, Normanno N, Ciardiello F and Tejpar S. KRAS, BRAF, PIK3CA, and PTEN mutations: implications for targeted therapies in metastatic colorectal cancer. Lancet Oncol 2011; 12: 594-603.

[35] Zeki SS, Graham TA and Wright NA. Stem cells and their implications for colorectal cancer. Nat Rev Gastroenterol Hepatol 2011; 8: 90-100.

[36] Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, Silliman N, Szabo S, Dezso Z, Ustyanksky V, Nikolskaya T, Nikolsky Y, Karchin R, Wilson PA, Kaminker JS, Zhang Z, Croshaw R, Willis J, Dawson D, Shipitsin M, Willson JK, Sukumar S, Polyak K, Park BH, Pethiyagoda CL, Pant PV, Ballinger DG, Sparks AB, Hartigan J, Smith DR, Suh E, Papadopoulos N, Buckhaults P, Markowitz SD, Parmigiani G, Kinzler KW, Velculescu VE and Vogelstein B. The genomic landscapes of human breast and colorectal cancers. Science 2007; 318: 1108-1113.

[37] Jones S, Chen WD, Parmigiani G, Diehl F, Beerenwinkel N, Antal T, Traulsen A, Nowak MA, Siegel C, Velculescu VE, Kinzler KW, Vogelstein B, Willis J and Markowitz SD. Comparative lesion sequencing provides insights into tumor evolution. Proc Natl Acad Sci U S A 2008; 105: 4283-4288.

[38] Mekenkamp LJ, Haan JC, Israeli D, van Essen HF, Dijkstra JR, van Cleef P, Punt CJ, Meijer GA, Nagtegaal ID and Ylstra B. Chromosomal copy number aberrations in colorectal metastases resemble their primary counterparts and differences are typically non-recurrent. PLoS One 2014; 9: e86833.

[39] Markowitz SD and Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. N Engl J Med 2009; 361: 2449-2460.

[40] Fodde R, Smits R and Clevers H. APC, signal transduction and genetic instability in colorectal cancer. Nat Rev Cancer 2001; 1: 55-67.

[41] Leary RJ, Lin JC, Cummins J, Boca S, Wood LD, Parsons DW, Jones S, Sjoblom T, Park BH, Parsons R, Willis J, Dawson D, Willson JK, Nikolskaya T, Nikolsky Y, Kopelovich L, Papadopoulos N, Pennacchio LA, Wang TL, Markowitz SD, Parmigiani G, Kinzler KW, Vogelstein B and Velculescu VE. Integrated analysis of homozygous deletions, focal amplifications, and sequence alterations in breast and colorectal cancers. Proc Natl Acad Sci U S A 2008; 105: 16224-16229.

[42] Sayagues JM, Abad Mdel M, Melchor HB, Gutierrez ML, Gonzalez-Gonzalez M, Jensen E, Bengoechea O, Fonseca E, Orfao A and Munoz-Bellvis L. Intratumoural cytogenetic heterogeneity of sporadic colorectal carcinomas suggests several pathways to liver metastasis. J Pathol 2010; 221: 308-319.

[43] Gonzalez-Gonzalez M, Fontanillo C, Abad MM, Gutierrez ML, Mota I, Bengoechea O, Santos-Briz A, Blanco O, Fonseca E, Ciudad J, Fuentes M, De Las Rivas J, Alcazar JA, Garcia J, Munoz-Bellvis L, Orfao A and Sayagues JM. Identification of a characteristic copy number alteration profile by high-resolution single nucleotide polymorphism arrays associated with metastatic sporadic colorectal cancer. Cancer 2014; 120: 1948-1959.

[44] Gutenberg A, Gerdes JS, Jung K, Sander B, Gunawan B, Bock HC, Liersch T, Bruck W, Rohde V and Fuzesi L. High chromosomal instability in brain metastases of colorectal carcinoma. Cancer Genet Cytogenet 2010; 198: 47-51.

[45] Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003; 3: 453-458.

[46] Sayagues JM, Fontanillo C, Abad Mdel M, Gonzalez-Gonzalez M, Sarasquete ME, Chillon Mdel C, Garcia E, Bengoechea O, Fonseca E, Gonzalez-Diaz M, De las Rivas J, Munoz-Bellvis L and Orfao A. Mapping of genetic abnormalities of primary tumours from metastatic CRC by high-resolution SNP arrays. PLoS One 2010; 5: e13752.

[47] Camps J, Morales C, Prat E, Ribas M, Capella G, Egozcue J, Peinado MA and Miro R. Genetic evolution in colon cancer KM12 cells and metastatic derivates. Int J Cancer 2004; 110: 869-874.

[48] Aschele C, Debernardis D, Lonardi S, Bandelloni R, Casazza S, Monfardini S and Gallo L. Deleted in colon cancer protein expression in colorectal cancer metastases: a major predictor of survival in patients with unresectable metastatic disease receiving palliative fluorouracil-based chemotherapy. J Clin Oncol 2004; 22: 3758-3765.

[49] Liu XP, Kawauchi S, Oga A, Sato T, Ikemoto K, Ikeda E and Sasaki K. Chromosomal aberrations detected by comparative genomic hybridization predict outcome in patients with colorectal carcinoma. Oncol Rep 2007; 17: 261-267.

[50] Knosel T, Schluns K, Stein U, Schwabe H, Schlag PM, Dietel M and Petersen I. Genetic imbalances with impact on survival in colorectal cancer patients. Histopathology 2003; 43: 323-331.

[51] Munoz-Bellvis L, Fontanillo C, Gonzalez-Gonzalez M, Garcia E, Iglesias M, Esteban C, Gutierrez ML, Abad MM, Bengoechea O, De Las Rivas J, Orfao A and Sayagues JM. Unique genetic profile of sporadic colorectal cancer liver metastasis versus primary tumors as defined by high-density single-nucleotide polymorphism arrays. Mod Pathol 2012; 25: 590-601.

[52] Kurashina K, Yamashita Y, Ueno T, Koinuma K, Ohashi J, Horie H, Miyakura Y, Hamada T, Haruta H, Hatanaka H, Soda M, Choi YL, Takada S, Yasuda Y, Nagai H and Mano H. Chromosome copy number analysis in screening for prognosis-related genomic regions in colorectal carcinoma. Cancer Sci 2008; 99: 1835-1840.

[53] Buffart TE, Coffa J, Hermsen MA, Carvalho B, van der Sijp JR, Ylstra B, Pals G, Schouten JP and Meijer GA. DNA copy number changes at 8q11-24 in metastasized colorectal cancer. Cell Oncol 2005; 27: 57-65.

[54] Bradbury J. Metastasis in colorectal cancer associated with phosphatase expression. Lancet 2001; 358: 1245.

[55] Marx J. Cancer research. New insights into metastasis. Science 2001; 294: 281-282.

[56] Nakao M, Kawauchi S, Furuya T, Uchiyama T, Adachi J, Okada T, Ikemoto K, Oga A and Sasaki K. Identification of DNA copy number aberrations associated with metastases of colorectal cancer using array CGH profiles. Cancer Genet Cytogenet 2009; 188: 70-76.

[57] Hidaka S, Yasutake T, Takeshita H, Kondo M, Tsuji T, Nanashima A, Sawai T, Yamaguchi H, Nakagoe T, Ayabe H and Tagawa Y. Differences in 20q13.2 copy number between colorectal cancers with and without liver metastasis. Clin Cancer Res 2000; 6: 2712-2717.

[58] Gilkes DM, Xiang L, Lee SJ, Chaturvedi P, Hubbi ME, Wirtz D and Semenza GL. Hypoxia-inducible factors mediate coordinated RhoA-ROCK1 expression and signaling in breast cancer cells. Proc Natl Acad Sci U S A 2014; 111: E384-393.

[59] Yu KD and Shao ZM. Initiation, evolution, phenotype and outcome of BRCA1 and BRCA2 mutation-associated breast cancer. Nat Rev Cancer 2012; 12: 372-373; author reply 372.

[60] Pinner S and Sahai E. PDK1 regulates cancer cell motility by antagonising inhibition of ROCK1 by RhoE. Nat Cell Biol 2008; 10: 127-137.

[61] Li J, Bharadwaj SS, Guzman G, Vishnubhotla R and Glover SC. ROCK I has more accurate prognostic value than MET in predicting patient survival in colorectal cancer. Anticancer Res 2015; 35: 3267-3273.

[62] Fackenthal JD and Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer 2007; 7: 937-948.

[63] Burki TK. BRCA1 and BRCA2 mutation type associated with cancer risk. Lancet Oncol 2015; 16: e205.
[64] Phelan CM, Iqbal J, Lynch HT, Lubinski J, Gronwald J, Moller P, Ghadirian P, Foulkes WD, Armel S, Eisen A, Neuhausen SL, Senter L, Singer CF, Ainsworth P, Kim-Sing C, Tung N, Llacuachaqui M, Chornokur G, Ping S, Narod SA; Hereditary Breast Cancer Study G. Incidence of colorectal cancer in BRCA1 and BRCA2 mutation carriers: results from a follow-up study. Br J Cancer 2014; 110: 530-534.
[65] Garre P, Martin L, Sanz J, Romero A, Tosar A, Bando I, Llovet P, Diaque P, Garcia-Paredes B, Diaz-Rubio E, de la Hoya M and Caldes T. BRCA2 gene: a candidate for clinical testing in familial colorectal cancer type X. Clin Genet 2015; 87: 582-587.
[66] Degrolard-Courcet E, Sokolowska J, Padeano MM, Guiu S, Bronner M, Chery C, Coron F, Lepage C, Chapusot C, Loustalot C, Jouve JL, Hatem C, Ferrant E, Martin L, Coutant C, Baurand A, Couillault G, Delignette A, El Chehadeh S, Lizard S, Arnould L, Fumoleau P, Callier P, Mugneret F, Philippe C, Frebourg T, Jonveaux P and Faivre L. Development of primary early-onset colorectal cancers due to biallelic mutations of the FANCD1/BRCA2 gene. Eur J Hum Genet 2014; 22: 979-987.
[67] Bernard-Gallon DJ, Peffault de Latour M, Hizel C, Vissac C, Cure H, Pezet D, Dechelotte PJ, Chipponi J, Chassagne J and Bignon YJ. Localization of human BRCA1 and BRCA2 in non-inherited colorectal carcinomas and matched normal mucosas. Anticancer Res 2001; 21: 2011-2020.
[68] Le Corre L, Vissac-Sabatier C, Chalabi N, Bignon YJ, Daver A, Chassevent A and Bernard-Gallon DJ. Quantitative analysis of BRCA1, BRCA2 and Hmsh2 mRNA expression in colorectal Lieberkuhnien adenocarcinomas and matched normal mucosa: relationship with cellular proliferation. Anticancer Res 2005; 25: 2009-2016.
[69] McConnell BB, Kim SS, Bialkowska AB, Yu K, Sitaraman SV and Yang VW. Kruppel-like factor 5 protects against dextran sulfate sodium-induced colonic injury in mice by promoting epithelial repair. Gastroenterology 2011; 140: 540-549 e542.
[70] McConnell BB, Klapproth JM, Sasaki M, Nandan MO and Yang VW. Kruppel-like factor 5 mediates transmissible murine colonic hyperplasia caused by Citrobacter rodentium infection. Gastroenterology 2008; 134: 1007-1016.
[71] Nandan MO, Ghaleb AM, Liu Y, Bialkowska AB, McConnell BB, Shroyer KR, Robine S and Yang VW. Inducible intestine-specific deletion of Kruppel-like factor 5 is characterized by a regenerative response in adult mouse colon. Dev Biol 2014; 387: 191-202.
[72] Shindo T, Manabe I, Fukushima Y, Tobe K, Aizawa K, Miyamoto S, Kawai-Kowase K, Moriyama N, Imai Y, Kawakami H, Nishimatsu H, Ishikawa T, Suzuki T, Morita H, Maemura K, Sata M, Hirata Y, Komukai M, Kagechika H, Kadowaki T, Kurabayashi M and Nagai R. Kruppel-like zinc-finger transcription factor KLF5/BTEB2 is a target for angiotensin II signaling and an essential regulator of cardiovascular remodeling. Nat Med 2002; 8: 856-863.
[73] Guo L, He P, No YR and Yun CC. Kruppel-like factor 5 incorporates into the beta-catenin/TCF complex in response to LPA in colon cancer cells. Cell Signal 2015; 27: 961-968.
[74] Bialkowska A, Crisp M, Madoux F, Spicer T, Knapinska A, Mercer B, Bannister TD, He Y, Chowdhury S, Cameron M, Yang VW and Hodder P. ML264: an antitumor agent that potently and selectively inhibits kruppel-like factor five (KLF5) expression: a probe for studying colon cancer development and progression. In: editors. Probe reports from the NIH molecular libraries program. Bethesda (MD): 2010. p.
[75] Bialkowska AB, Du Y, Fu H and Yang VW. Identification of novel small-molecule compounds that inhibit the proproliferative Kruppel-like factor 5 in colorectal cancer cells by high-throughput screening. Mol Cancer Ther 2009; 8: 563-570.
[76] Baker AM, Bird D, Lang G, Cox TR and Erler JT. Lysyl oxidase enzymatic function increases stiffness to drive colorectal cancer progression through FAK. Oncogene 2013; 32: 1863-1868.
[77] Sun C, Zargham R, Shao Q, Gui X, Marcus V, Lazaris A, Salman A, Metrakos P, Qu X and Gao Z. Association of CD98, integrin beta1, integrin beta3 and Fak with the progression and liver metastases of colorectal cancer. Pathol Res Pract 2014; 210: 668-674.
[78] Garouniatis A, Zizi-Sermpetzoglou A, Rizos S, Kostakis A, Nikiteas N and Papavassiliou AG. FAK, CD44v6, c-Met and EGFR in colorectal cancer parameters: tumour progression, metastasis, patient survival and receptor crosstalk. Int J Colorectal Dis 2013; 28: 9-18.
[79] McCarthy N. Tumorigenesis: Megaphone MYC. Nat Rev Cancer 2012; 12: 733.
[80] Wiegering A, Uthe FW, Jamieson T, Ruoss Y, Huttenrauch M, Kuspert M, Pfann C, Nixon C, Herold S, Walz S, Taranets L, Germer CT, Rosenwald A, Sansom OJ and Eilers M. Targeting translation initiation bypasses signaling crosstalk mechanisms that maintain high MYC levels in colorectal cancer. Cancer Discov 2015; 5: 768-781.

[81] Toon CW, Chou A, Clarkson A, DeSilva K, Houang M, Chan JC, Sioson LL, Jankova L and Gill AJ. Immunohistochemistry for myc predicts survival in colorectal cancer. PLoS One 2014; 9: e87456.

[82] Sanchez-Pernaute A, Perez-Aguirre E, Cerdan FJ, Iniesta P, Diez Valladares L, de Juan C, Moran A, Garcia-Botella A, Garcia Aranda C, Benito M, Torres AJ and Balibrea JL. Overexpression of c-myc and loss of heterozygosity on 2p, 3p, 5q, 17p and 18q in sporadic colorectal carcinoma. Rev Esp Enferm Dig 2005; 97: 169-178.

[83] Ben-David E, Bester AC, Shifman S and Kerem B. Transcriptional dynamics in colorectal carcinogenesis: new insights into the role of c-Myc and miR17 in benign to cancer transformation. Cancer Res 2014; 74: 5532-5540.

[84] Al-Kuraya K, Novotny H, Bavi P, Siraj AK, Uddin S, Ezzat A, Sanea NA, Al-Dayel F, Al-Mana H, Sheikh SS, Mirlacher M, Tapia C, Simon R, Sauter G, Terracciano L and Tornillo L. HER2, TOP2A, CCND1, EGFR and C-MYC oncogene amplification in colorectal cancer. J Clin Pathol 2007; 60: 768-772.

[85] Zalata KR, Elshal MF, Foda AA and Shoma A. Genetic dissimilarity between primary colorectal carcinomas and their lymph node metastases: ploidy, p53, bcl-2, and c-myc expression-a pilot study. Tumour Biol 2015; 36: 6579-84.

[86] Obara K, Yokoyama M, Asano G and Tanaka S. Evaluation of myc and chromosome 8 copy number in colorectal cancer using interphase cytogenetics. Int J Oncol 2001; 18: 233-239.

[87] Wang B, Hsu SH, Wang X, Kutay H, Bid HK, Yu J, Ganju RK, Jacob ST, Yuneva M and Ghoshal K. Reciprocal regulation of microRNA-122 and c-Myc in hepatocellular cancer: role of E2F1 and transcription factor dimerization partner 2. Hepatology 2014; 59: 555-566.

[88] Coulouarn C, Factor VM, Andersen JB, Durkin ME and Thorgeirsson SS. Loss of miR-122 expression in liver cancer correlates with suppression of the hepatic phenotype and gain of metastatic properties. Oncogene 2009; 28: 3526-3536.

[89] Fong MY, Zhou W, Liu L, Alontaga AY, Chandra M, Ashby J, Chow A, O'Connor ST, Li S, Chin AR, Somlo G, Palomares M, Li Z, Tremblay JR, Tsuyada A, Sun G, Reid MA, Wu X, Swiderski P, Ren X, Shi Y, Kong M, Zhong W, Chen Y and Wang SE. Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis. Nat Cell Biol 2015; 17: 183-194.

[90] He J, Xie G, Tong J, Peng Y, Huang H, Li J, Wang N and Liang H. Overexpression of microRNA-122 re-sensitizes 5-FU-resistant colon cancer cells to 5-FU through the inhibition of PKM2 in vitro and in vivo. Cell Biochem Biophys 2014; 70: 1343-1350.

[91] Iino I, Kikuchi H, Miyazaki S, Hiramatsu Y, Ohta M, Kamiya K, Kusama Y, Baba S, Setou M and Konno H. Effect of miR-122 and its target gene cationic amino acid transporter 1 on colorectal liver metastasis. Cancer Sci 2013; 104: 624-630.