

Figure 2 Molecular pathway for microsatellite instability+ gastric cancer. The model for the carcinogenesis of microsatellite instability (MSI)⁺ gastric cancer is presented. CIMP: CpG island methylator phenotype.

loss of ARID1A may be involved in the progression of EBV/MSI GCs. Thus, loss of ARID1A appears to have different, pathway-dependent roles in GC.

WHOLE-GENOME SEQUENCING ANALYSIS OF GC

To explore the complete list of somatic alterations in GC, Nagarajan *et al.*^[34] combined massively parallel short read and DNA paired-end tag sequencing for the first whole-genome analysis of two GCs, one with CIN and the other with MSI. Integrative analysis and de novo assemblies revealed the architecture of a wild-type KRAS amplification, a common driver event in GC^[35]. Three distinct mutational signatures were discovered against a genome-wide backdrop of oxidative and MSI-associated mutational signatures. Combining sequencing data from 40 complete GC exomes and targeted screening of an additional 94 independent GCs led to the discovery of ACVR2A, RPL22 and LMAN1 as recurrently mutated genes in MSI⁺ GC and the identification of PAPPA as a recurrently mutated gene in TP53 wild-type GC. These results highlight how whole-genome sequencing analysis can provide relevant information about tissue-specific carcinogenesis that would otherwise be missed in exome-sequencing data. WGS of more GCs will uncover more recurrently altered genes.

miRNA alterations

A microRNA (miRNA) is a small noncoding RNA that regulates gene expression at the posttranscriptional level and is critical in many biological processes and cellular

pathways^[36-40]. The causes of aberrant miRNA expression patterns in cancer include DNA copy number amplification or deletion, inappropriate transactivation, transcriptional repression by oncogenic and other factors, failure of miRNA post-transcriptional regulation and genetic mutation or transcriptional silencing associated with hypermethylation of the CpG island promoters.

There is accumulating evidence to support the notion that miRNA alterations play a key role in the pathogenesis of GC^[41-44]. A large number of miRNAs with different biological functions have been found to be altered and correlated with clinicopathological characteristics and/or prognosis in GC. Moreover, the clinical potential of miRNA alterations as minimally invasive diagnostic biomarkers and therapeutic targets has been extensively reported^[37,40,42,44]. Recent studies have shown that tumor-derived miRNAs are present and stable in circulation, and the levels of circulating miRNAs are detectable and quantifiable. Both tissue and soluble miRNAs are candidates for diagnostic biomarkers and therapeutic targets in GCs^[44]. The basic strategy of current miRNA-based treatment studies is to either antagonize the expression of target oncogenic miRNAs with antisense therapy and other technology or to restore the function of impaired tumor suppressor miRNAs^[42].

The inclusion of different isoforms of miRNA (isomiRs) that are natural variants of mature miRNAs will form a detailed miRnome. Because expression of isomiRs can be estimated by NGS, NGS platforms provide the most effective method of miRNA profiling, leading to the identification of the miRNA alterations with clinical applications. Li *et al.*^[45] sequenced small RNAs from one pair of GC and noncancerous tissue and found that isomiR patterns are significantly different between these tissues. Moreover, these authors found that the 5p arm and 3p arm miRNAs derived from the same pre-miRNAs have different tissue preferences in GC and noncancerous tissue, suggesting a novel mechanism regulating mature miRNA selection.

WHOLE-TRANSCRIPTOME SEQUENCING OF GC

The first comprehensive RNA-seq study in GC has been recently published. Kim *et al.*^[46] applied a whole-transcriptome sequencing approach to 24 GC samples and six noncancerous tissue specimens. Importantly, these authors developed a multilayered integrative analysis to identify various types of transcriptional aberrations, such as differentially expressed mRNAs and miRNAs, as well as recurrently mutated genes. A central metabolic regulator gene, AMPKa2 (PRKAA2), was identified as a potential functional target in GC. Six key miRNAs (miR-548d-3p, miR-20b, miR-135b, miR-140-3p, miR-93 and miR-19a) in GC were also identified.

Epigenetic alterations

Epigenetic regulation is essential for the normal develop-

ment and maintenance of tissue-specific gene expression patterns in mammals. Disruption of epigenetic regulation can lead to altered gene function and malignant cellular transformation^[47]. Recent cancer epigenetic studies have revealed various alterations in the epigenetic machinery in GC, including DNA methylation, histone modifications, nucleosome positioning, noncoding RNAs and miRNAs^[48-52]. Aberrant DNA methylation in the promoter CpG islands of genes results in inactivation of tumor suppressor and other tumor-related genes in cancer cells and is the most well-defined epigenetic hallmark in GC. Methylation of a large number of genes with different biological functions has been found to be correlated with the clinicopathological characteristics and prognosis in GC^[48-52]. DNA methylation with its advantages as a biomarker for the detection of cancer in biopsy specimens and body fluids that can be obtained non-invasively, such as serum and gastric washes, may have a clinical application in GC. Detection of aberrant DNA methylation of genes, such as *CDH1*, *DAPK*, *GSTP1*, *p15*, *p16*, *RARβ*, *RASSF1A*, *RUNX3* and *TFPI2*, in the serum may be a useful biomarker for the detection of GC^[50]. Studies of DNA methylation and histone modification using NGS technologies, such as whole-genome bisulfite sequencing and targeted bisulfite sequencing, will lead to new discoveries and improve our knowledge of the epigenomics of GC^[11].

Association of the aberrant methylation of RASGRF1 with an epigenetic field defect and an increased risk of GC

Aberrant DNA methylation is implicated in the epigenetic field defect seen in GC. Thus, it is important to identify predictive biomarkers by screening for DNA methylation in the noncancerous background gastric mucosa of patients with GC. Using methylated-CpG island amplification coupled with CpG island microarray (MCAM) analysis, Takamaru *et al.*^[53] found 224 genes that were methylated in the noncancerous gastric mucosa of patients with GC. Among them, RASGRF1 methylation was significantly elevated in the gastric mucosa from patients with either intestinal- or diffuse-type GC, compared with the mucosa from healthy individuals. RASGRF1 methylation was independent of mucosal atrophy and could be used to distinguish both serum pepsinogen test-positive and -negative patients with GC from healthy individuals. Ectopic expression of RASGRF1 suppressed colony formation and Matrigel invasion by GC cells. RASGRF1 methylation appears to be significantly involved in the epigenetic field defect of the stomach and to be a useful biomarker to identify individuals at high risk for GC.

Association of aberrant methylation of miR-34b/c with an epigenetic field defect and an increased risk of GC

The silencing of miRNAs is often associated with CpG island hypermethylation. Thus, to identify epigenetically silenced miRNAs in GC, Suzuki *et al.*^[54] screened

for miRNAs that were induced by treatment of GC cells with 5-aza-2'-deoxycytidine and 4-phenylbutyrate. Hypermethylation of the neighboring CpG island epigenetically silenced miR-34b and miR-34c. Methylation of the miR-34b/c CpG island was frequently observed in GC cell lines (13/13, 100%) but not in normal gastric mucosa from healthy *H. pylori*-negative individuals. Transfection of the precursors of miR-34b and miR-34c into GC cells suppressed growth and changed the gene expression profile. Methylation of miR-34b/c was found in a majority of primary GCs (83/118, 70%). Notably, analysis of the non-cancerous gastric mucosae from GC patients ($n = 109$) and healthy individuals ($n = 85$) revealed that methylation levels were higher in the gastric mucosae of patients with multiple GC lesions than in the mucosae from those patients with single GC and the mucosae from healthy *H. pylori*-positive individuals. These results suggest that miR-34b and miR-34c are novel tumor suppressors frequently silenced by DNA methylation in GC. Methylation of miR-34b/c appears to be significantly involved in an epigenetic field defect in the stomach and to be a useful biomarker to identify individuals at high risk for multiple GC.

Methylation of miR-34b/c in the mucosa of the noncancerous gastric body may be a useful biomarker for predicting the risk of metachronous GC

Metachronous GC can develop after endoscopic resection of GC and is not predictable based on the clinical characteristics alone. Aberrant DNA methylation in noncancerous gastric mucosa has been implicated in gastric carcinogenesis and may be a useful biomarker of GC risk. Suzuki *et al.*^[55] evaluated the clinical utility of DNA methylation as a biomarker of metachronous GC risk. Scheduled follow-up endoscopy was performed in 129 patients after curative endoscopic resection of early GC. Biopsy specimens were collected from noncancerous mucosa in the gastric antrum and body. A quantitative methylation analysis of miR-34b/c, SFRP1, SFRP2, SFRP5, DKK2 and DKK3 using bisulfite pyrosequencing was performed on the collected biopsy specimens. The utility of the methylation status for predicting the risk of developing metachronous GC was analyzed using Kaplan-Meier and Cox proportional hazards models. During the follow-up period, 17 patients (13%) developed metachronous GCs. The cumulative incidence of metachronous GC was significantly higher among patients with elevated miR-34b/c, SFRP2 and DKK2 methylation in the gastric body. Elevated methylation of miR-34b/c showed the most significant association with the risk of metachronous GC; the cumulative incidence of metachronous GC was much higher in the high miR-34b/c-methylation group than in the low methylation group. Multivariate analysis adjusted for age, sex, *H. pylori* status and pathological findings showed that miR-34b/c methylation in the gastric body was an independent predictor of metachronous GC risk. Methylation of miR-34b/c in the mucosa of the noncancerous gastric

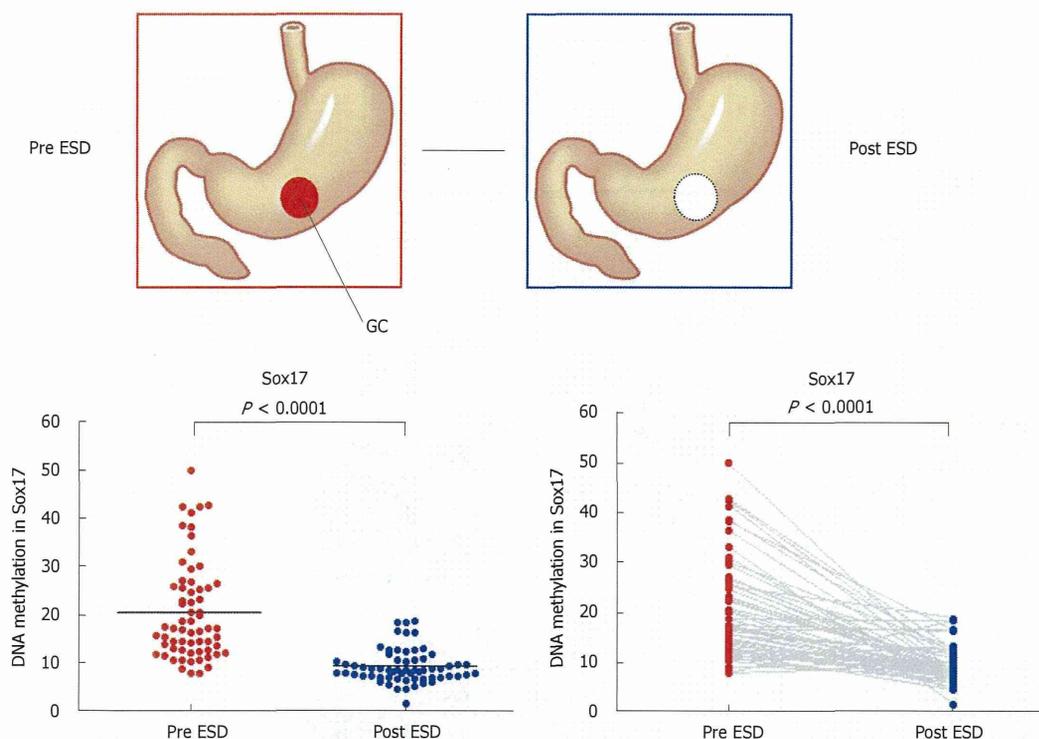


Figure 3 Methylation levels of Sox17 before and after endoscopic submucosal dissection. Methylation levels of Sox17 were analyzed by pyrosequencing using the DNA recovered from gastric washes before and after endoscopic submucosal dissection^[57].

body may be a useful biomarker for predicting the risk of metachronous GC. Finally, NGS technologies may characterize an epigenetic field defect more clearly and highlight more useful biomarkers.

Sensitive and specific detection of early GC by DNA methylation analysis of gastric washes

Because many mucosal cells can be found in the gastric juice, the detection of molecular markers in the gastric juice was a possible noninvasive approach to detect GC. However, the use of gastric juice as a molecular diagnostic or predictive tool has been previously reported to be impractical because the DNA is easily degraded by gastric acidity. In this regard, Watanabe *et al.*^[56] have developed a new method for GC detection by DNA methylation in gastric washes but not in gastric juice. These authors analyzed 51 candidate genes in 7 GC cell lines and 24 GC samples (training set). They then selected 6 genes (*MINT25*, *RORA*, *GDNF*, *ADAM23*, *PRDM5* and *MLF1*) for further analyses. The methylation status of these genes was analyzed in a test set consisting of 131 GCs at various stages. The 6 candidate genes were validated in a different population of 40 primary GC samples and 113 noncancerous gastric mucosa samples. The 6 genes showed differential methylation in GC and normal mucosa in the training, test and validation sets. *GDNF* and *MINT25* were the most sensitive molecular markers of early-stage GC, whereas *PRDM5* and *MLF1* were markers of a field defect. A close correlation be-

tween methylation levels in tumor biopsy samples and gastric washes was noted. *MINT25* methylation showed the best sensitivity (90%) and specificity (96%), and it had the greatest area under the receiver operating characteristic curve (0.961) in terms of tumor detection in gastric washes. *MINT25* methylation in gastric washes may be a sensitive and specific marker for the screening of GC.

Detection of early GC by DNA methylation analysis of Sox17 in gastric washes

Although minimally invasive treatment is widely accepted for early-stage GC, appropriate risk markers to detect residual cancer after endoscopic resection and the potential for recurrence are not available. To find candidate genes that might be markers for the detection of early GC, Oishi *et al.*^[57] performed methylated CpG island amplification microarray analysis on 12 gastric washes (from the pre- and post-endoscopic treatment of six patients). Among the candidate genes, the *Sox17* gene was selected for further analysis. The DNA methylation status of *Sox17* was examined in a validation set consisting of 128 gastric wash samples (64 pre-treatment and 64 post-treatment) from cases of early GC. *Sox17* showed significant differential methylation in the pre- and post-treatment gastric washes of early GC patients (Figure 3). Moreover, the treatment of GC cells that lacked *Sox17* expression with the methyltransferase inhibitor 5-aza-2'-deoxycytidine restored the gene's expression. Additionally, the introduction of exogenous *Sox17* into silenced

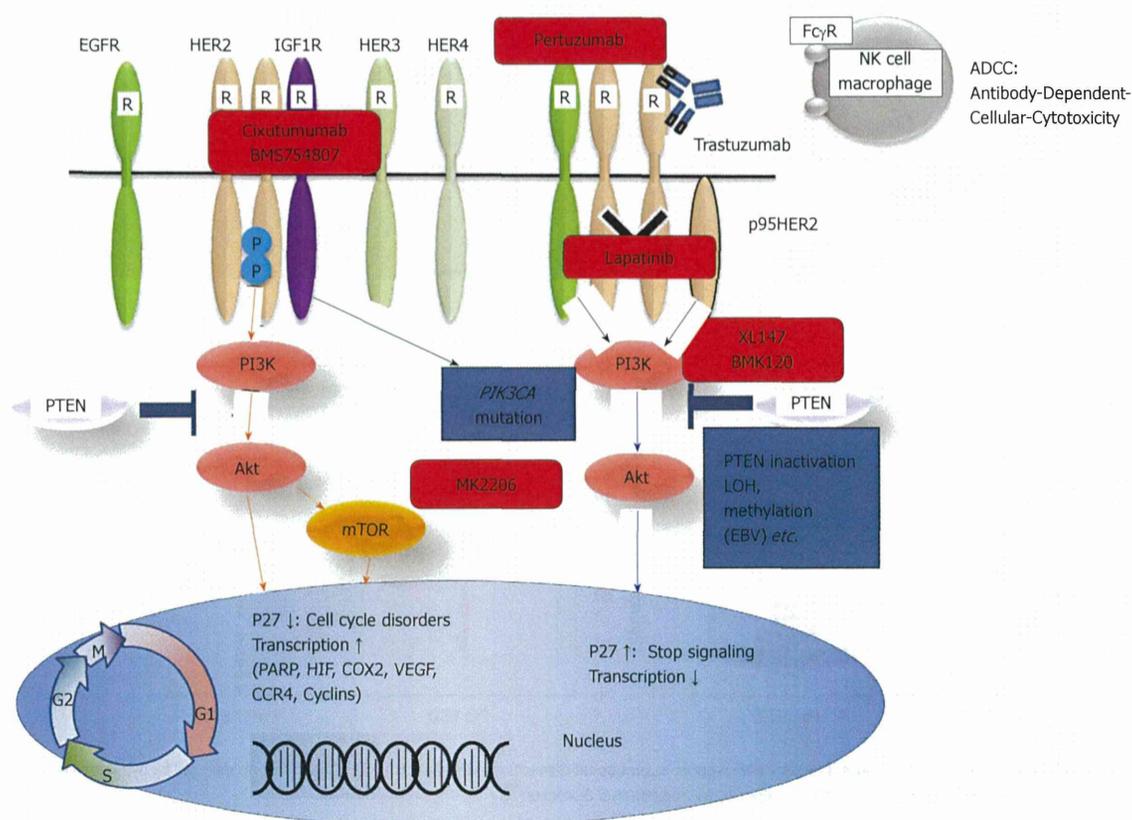


Figure 4 Human epidermal growth receptor family members, the PI3K/Akt pathway, and targeted drugs. HER: Human epidermal growth receptor; NK: Natural killer; IGF1R: α -insulin-like growth factor 1-receptor; EGFR: Epidermal growth factor receptor; PI3K: Phosphatidylinositol-3-kinase; PTEN: Phosphatase and tensin homologue.

GC cells suppressed colony formation. The data suggest that the silencing of Sox17 occurs frequently in early GC and plays a key role in the disease. Gastric wash-based DNA methylation analysis could be useful for the early detection of recurrence following endoscopic resection in early GC patients. Interestingly, the usefulness of gastric wash-based molecular testing for antibiotic resistance in *H. pylori* has also been reported^[58]. It will be interesting to analyze gastric washes using NGS.

Anti-HER2 antibody trastuzumab has led to an era of personalized therapy in GC

Trastuzumab is an antibody that targets the HER2 extracellular domain and induces antibody-dependent cellular cytotoxicity and inhibition of the HER2 downstream signals (Figure 4). In the ToGA study, standard chemotherapy regimens (capecitabine plus cisplatin or fluorouracil plus cisplatin) combined with trastuzumab resulted in a longer survival time than standard regimens without trastuzumab in patients with HER2-positive GC^[59]. Thus, HER2 expression has become a major concern in GC^[60]. HER2 overexpression is observed in 7%-34% of GC cases. Mechanisms of resistance to trastuzumab have been reported in breast cancer. There are various mechanisms underlying trastuzumab resistance, such as alterations of the HER2 structure or surroundings,

dysregulation of HER2 downstream signal effectors and interaction of HER2 with other membrane receptors (Figure 4). The PI3K-Akt pathway is one of the main downstream signaling pathways of HER2. It is well known that PIK3CA mutations and PTEN inactivation cause over-activation of a downstream signal without activation of an upstream signal. The frequencies of PIK3CA mutations and PTEN inactivation in GC have been reported to be 4%-25% and 16%-77%, respectively. However, little is known about the association between HER2 expression and PI3K-Akt pathway alterations in GC. Sukawa *et al.*^[29] have found that HER2 overexpression was significantly correlated with pAkt expression in GC tissues. Furthermore, pAkt expression was correlated with poor prognosis. These results suggest that the PI3K-Akt pathway plays an important role in HER2-positive GC. Moreover, PIK3CA mutations and PTEN inactivation could affect the effectiveness of HER2-targeting therapy. Thus, it is necessary to clarify not only HER2 alterations but also PI3K-Akt pathway alterations to optimize HER2-targeting therapy in patients with GC. In this regard, NGS will be useful for the identification of complicated mechanisms of trastuzumab resistance in GC. The only approved targeted therapy for patients with advanced GC is trastuzumab. It is hoped that NGS will reveal a driver gene alteration that will make other targeted

therapies possible^[13,61].

Monoclonal antibodies targeting VEGF (AVAGAST trial) and VEGFR-2 (REGARD trial) in advanced GC

Several vascular endothelial growth factor (VEGF)-targeted agents have been developed, including neutralizing monoclonal antibodies (MoAbs) to VEGF/VEGFRs, soluble VEGF receptors and tyrosine kinase inhibitors (TKIs). The anti-VEGF MoAb bevacizumab has been approved for colorectal cancers. VEGF and VEGF receptor-2 (VEGFR-2)-mediated signaling and angiogenesis contribute to the pathogenesis and progression of GC. The Avastin in Gastric Cancer (AVAGAST) trial was a multinational, randomized, placebo-controlled trial designed to evaluate the efficacy of adding bevacizumab to capecitabine-cisplatin in the first-line treatment of advanced GC^[62]. The study showed that adding bevacizumab to the chemotherapy regimen in patients with advanced GC improved the progression-free survival and tumor response rate but not the overall survival. A following biomarker evaluation analysis revealed that plasma VEGF-A and tumor neuropilin-1 are strong biomarker candidates for predicting the clinical outcome in patients with advanced GC treated with bevacizumab^[63]. In this regard, NGS will be a powerful method for the identification of predictive biomarkers.

To analyze whether ramucirumab, a monoclonal antibody targeting VEGFR-2, prolongs survival in patients with advanced GC, an international, randomized, double-blind, placebo-controlled, phase 3 trial was conducted in 29 countries^[64]. In total, 355 patients with advanced gastric or gastro-esophageal junction adenocarcinoma and disease progression after first-line chemotherapy were randomly assigned (2:1) to receive best supportive care plus either ramucirumab 8 mg/kg ($n = 238$) or placebo ($n = 117$), intravenously once every 2 wk. The primary endpoint was overall survival. The median overall survival was 5.2 mo in the ramucirumab group and 3.8 mo in the placebo group (HR = 0.776, 95%CI: 0.603-0.998, $P = 0.047$). The survival benefit with ramucirumab remained unchanged after multivariate adjustment for other prognostic factors (multivariate HR = 0.774, 95%CI: 0.605-0.991, $P = 0.042$). Thus, ramucirumab is the first biological treatment given as a single drug that showed survival benefits in patients with advanced gastric or gastro-esophageal junction adenocarcinoma who progressed after first-line chemotherapy. The findings also validate VEGFR-2 signaling as an important therapeutic target in advanced GC.

Potential targeted drugs for GC

Using NGS to target a subset of druggable genes becomes a more effective way to discover therapeutic targets^[13,14,61]. There are several potential targeted drugs, either MoAb or small-molecule TKIs, that are being investigated either in synergy with, or in place of, established treatments. These drugs include inhibitors of growth factors and their receptors [*i.e.*, VEGF, epidermal growth factor receptor, HER2, insulin-like growth factor

1 (IGF1) receptor, c-MET], MEK inhibitors and drugs targeting the Hedgehog pathway^[65].

Dysregulation of the IGF1 and IGF2/IGF1R system has been implicated in the pathogenesis of GC^[66-69]. The expression levels of both IGFs and IGF1R are increased in GC. IGF1R is also involved in angiogenesis and lymphangiogenesis through the modulation of VEGF expression in a GC cell line^[70]. IGF1R blockade reduced tumor angiogenesis and enhanced the effects of bevacizumab in a GC cell line. Thus, targeting IGF1R in combination with agents that block the VEGF pathway may have therapeutic utility in GC. Moreover, targeting the novel miR-7/IGF1R/Snail axis has been reported to be useful as a therapeutic approach to block GC metastasis^[71].

CONCLUSION

The genetic and epigenetic alterations in GCs continue to inspire biological and clinical implications. Recent advances in the molecular study of GC have brought new diagnostic and therapeutic strategies into clinical settings. The advantages of using DNA methylation as a biomarker for the detection of GC in biopsy specimens and non-invasive body fluids such as serum and gastric washes may have a possible clinical application in GC. Further analysis is required to gain a deeper insight into GC carcinogenesis, a better understanding of disease pathogenesis and the development of new diagnostic and therapeutic approaches targeting essential pathogenic alterations. In this regard, the rapid advances in NGS technologies will hopefully continue to reveal driver alterations of GC, further our understanding of gastric carcinogenesis and improve the therapy for each individual tumor. The characterization of genes that were discovered by NGS rather than by laboratory and clinical research is also necessary.

REFERENCES

- 1 Wadhwa R, Song S, Lee JS, Yao Y, Wei Q, Ajani JA. Gastric cancer-molecular and clinical dimensions. *Nat Rev Clin Oncol* 2013; **10**: 643-655 [PMID: 24061039 DOI: 10.1038/nrclinonc.2013.170]
- 2 Akhavan-Niaki H, Samadani AA. Molecular Insight in Gastric Cancer Induction: An Overview of Cancer Stemness Genes. *Cell Biochem Biophys* 2013 Sep 28; Epub ahead of print [PMID: 24078401]
- 3 Figueiredo C, Garcia-Gonzalez MA, Machado JC. Molecular pathogenesis of gastric cancer. *Helicobacter* 2013; **18** Suppl 1: 28-33 [PMID: 24011242 DOI: 10.1111/hel.12083]
- 4 Conteduca V, Sansonno D, Lauletta G, Russi S, Ingravallo G, Dammacco F. H. pylori infection and gastric cancer: state of the art (review). *Int J Oncol* 2013; **42**: 5-18 [PMID: 23165522 DOI: 10.3892/ijo.2012.1701]
- 5 Yamamoto E, Suzuki H, Takamaru H, Yamamoto H, Toyota M, Shinomura Y. Role of DNA methylation in the development of diffuse-type gastric cancer. *Digestion* 2011; **83**: 241-249 [PMID: 21273772 DOI: 10.1159/000320453]
- 6 Baker AM, Graham TA, Wright NA. Pre-tumour clones, periodic selection and clonal interference in the origin and progression of gastrointestinal cancer: potential for biomarker development. *J Pathol* 2013; **229**: 502-514 [PMID: 23288692 DOI: 10.1002/path.4157]
- 7 Meyerson M, Gabriel S, Getz G. Advances in understanding

- cancer genomes through second-generation sequencing. *Nat Rev Genet* 2010; **11**: 685-696 [PMID: 20847746 DOI: 10.1038/nrg2841]
- 8 **Mardis ER.** A decade's perspective on DNA sequencing technology. *Nature* 2011; **470**: 198-203 [PMID: 21307932 DOI: 10.1038/nature09796]
 - 9 **Patel LR, Nykter M, Chen K, Zhang W.** Cancer genome sequencing: understanding malignancy as a disease of the genome, its conformation, and its evolution. *Cancer Lett* 2013; **340**: 152-160 [PMID: 23111104 DOI: 10.1016/j.canlet.2012.10.018]
 - 10 **Lawrence MS, Stojanov P, Mermel CH, Robinson JT, Garraway LA, Golub TR, Meyerson M, Gabriel SB, Lander ES, Getz G.** Discovery and saturation analysis of cancer genes across 21 tumour types. *Nature* 2014; **505**: 495-501 [PMID: 24390350 DOI: 10.1038/nature12912]
 - 11 **Lee EJ, Luo J, Wilson JM, Shi H.** Analyzing the cancer methylome through targeted bisulfite sequencing. *Cancer Lett* 2013; **340**: 171-178 [PMID: 23200671 DOI: 10.1016/j.canlet.2012.10.040]
 - 12 **Martens-Uzunova ES, Olvedy M, Jenster G.** Beyond microRNA--novel RNAs derived from small non-coding RNA and their implication in cancer. *Cancer Lett* 2013; **340**: 201-211 [PMID: 23376637 DOI: 10.1016/j.canlet.2012.11.058]
 - 13 **Xuan J, Yu Y, Qing T, Guo L, Shi L.** Next-generation sequencing in the clinic: promises and challenges. *Cancer Lett* 2013; **340**: 284-295 [PMID: 23174106 DOI: 10.1016/j.canlet.2012.11.025]
 - 14 **Ulahannan D, Kovac MB, Mulholland PJ, Cazier JB, Tomlinson I.** Technical and implementation issues in using next-generation sequencing of cancers in clinical practice. *Br J Cancer* 2013; **109**: 827-835 [PMID: 23887607 DOI: 10.1038/bjc.2013.416]
 - 15 **Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, Martinez P, Matthews N, Stewart A, Tarpey P, Varela I, Phillimore B, Begum S, McDonald NQ, Butler A, Jones D, Raine K, Latimer C, Santos CR, Nohadani M, Eklund AC, Spencer-Dene B, Clark G, Pickering L, Stamp G, Gore M, Szallasi Z, Downward J, Futreal PA, Swanton C.** Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012; **366**: 883-892 [PMID: 22397650 DOI: 10.1056/NEJMoa1113205]
 - 16 **Meacham CE, Morrison SJ.** Tumour heterogeneity and cancer cell plasticity. *Nature* 2013; **501**: 328-337 [PMID: 24048065 DOI: 10.1038/nature12624]
 - 17 **Horswell S, Matthews N, Swanton C.** Cancer heterogeneity and "the struggle for existence": diagnostic and analytical challenges. *Cancer Lett* 2013; **340**: 220-226 [PMID: 23142290 DOI: 10.1016/j.canlet.2012.10.031]
 - 18 **Liang H, Kim YH.** Identifying molecular drivers of gastric cancer through next-generation sequencing. *Cancer Lett* 2013; **340**: 241-246 [PMID: 23178814 DOI: 10.1016/j.canlet.2012.11.029]
 - 19 **Yamamoto H, Imai K, Perucho M.** Gastrointestinal cancer of the microsatellite mutator phenotype pathway. *J Gastroenterol* 2002; **37**: 153-163 [PMID: 11931527]
 - 20 **Perucho M.** Tumors with microsatellite instability: many mutations, targets and paradoxes. *Oncogene* 2003; **22**: 2223-2225 [PMID: 12700658 DOI: 10.1038/sj.onc.1206580]
 - 21 **Imai K, Yamamoto H.** Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis* 2008; **29**: 673-680 [PMID: 17942460 DOI: 10.1093/carcin/bgm228]
 - 22 **Yamamoto H, Adachi Y, Taniguchi H, Kunimoto H, Noshok K, Suzuki H, Shinomura Y.** Interrelationship between microsatellite instability and microRNA in gastrointestinal cancer. *World J Gastroenterol* 2012; **18**: 2745-2755 [PMID: 22719182 DOI: 10.3748/wjg.v18.i22.2745]
 - 23 **Ropero S, Fraga MF, Ballestar E, Hamelin R, Yamamoto H, Boix-Chornet M, Caballero R, Alaminos M, Setien F, Paz MF, Herranz M, Palacios J, Arango D, Orntoft TF, Aaltonen LA, Schwartz S, Esteller M.** A truncating mutation of HDAC2 in human cancers confers resistance to histone deacetylase inhibition. *Nat Genet* 2006; **38**: 566-569 [PMID: 16642021 DOI: 10.1038/ng1773]
 - 24 **Melo SA, Ropero S, Moutinho C, Aaltonen LA, Yamamoto H, Calin GA, Rossi S, Fernandez AF, Carneiro F, Oliveira C, Ferreira B, Liu CG, Villanueva A, Capella G, Schwartz S, Shiekhhattar R, Esteller M.** A TARBP2 mutation in human cancer impairs microRNA processing and DICER1 function. *Nat Genet* 2009; **41**: 365-370 [PMID: 19219043 DOI: 10.1038/ng.317]
 - 25 **Melo SA, Moutinho C, Ropero S, Calin GA, Rossi S, Spizzo R, Fernandez AF, Davalos V, Villanueva A, Montoya G, Yamamoto H, Schwartz S, Esteller M.** A genetic defect in exportin-5 traps precursor microRNAs in the nucleus of cancer cells. *Cancer Cell* 2010; **18**: 303-315 [PMID: 20951941 DOI: 10.1016/j.ccr.2010.09.007]
 - 26 **Kim TM, Laird PW, Park PJ.** The landscape of microsatellite instability in colorectal and endometrial cancer genomes. *Cell* 2013; **155**: 858-868 [PMID: 24209623 DOI: 10.1016/j.cell.2013.10.015]
 - 27 **Wang K, Kan J, Yuen ST, Shi ST, Chu KM, Law S, Chan TL, Kan Z, Chan AS, Tsui WY, Lee SP, Ho SL, Chan AK, Cheng GH, Roberts PC, Rejto PA, Gibson NW, Pocalyko DJ, Mao M, Xu J, Leung SY.** Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. *Nat Genet* 2011; **43**: 1219-1223 [PMID: 22037554 DOI: 10.1038/ng.982]
 - 28 **Zang ZJ, Cutcutache I, Poon SL, Zhang SL, McPherson JR, Tao J, Rajasegaran V, Heng HL, Deng N, Gan A, Lim KH, Ong CK, Huang D, Chin SY, Tan IB, Ng CC, Yu W, Wu Y, Lee M, Wu J, Poh D, Wan WK, Rha SY, So J, Salto-Tellez M, Yeoh KG, Wong WK, Zhu YJ, Futreal PA, Pang B, Ruan Y, Hillmer AM, Bertrand D, Nagarajan N, Rozen S, Teh BT, Tan P.** Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes. *Nat Genet* 2012; **44**: 570-574 [PMID: 22484628 DOI: 10.1038/ng.2246]
 - 29 **Sukawa Y, Yamamoto H, Noshok K, Kunimoto H, Suzuki H, Adachi Y, Nakazawa M, Nobuoka T, Kawayama M, Mikami M, Matsuno T, Hasegawa T, Hirata K, Imai K, Shinomura Y.** Alterations in the human epidermal growth factor receptor 2-phosphatidylinositol 3-kinase-v-Akt pathway in gastric cancer. *World J Gastroenterol* 2012; **18**: 6577-6586 [PMID: 23236232 DOI: 10.3748/wjg.v18.i45.6577]
 - 30 **Sukawa Y, Yamamoto H, Noshok K, Ito M, Igarashi H, Naito T, Mitsuhashi K, Matsunaga Y, Takahashi T, Mikami M, Adachi Y, Suzuki H, Shinomura Y.** HER2 expression and PI3K-Akt pathway alterations in gastric cancer. *Digestion* 2014; **89**: 12-17 [PMID: 24458107 DOI: 10.1159/000356201]
 - 31 **Holbrook JD, Parker JS, Gallagher KT, Halsey WS, Hughes AM, Weigman VJ, Lebowitz PF, Kumar R.** Deep sequencing of gastric carcinoma reveals somatic mutations relevant to personalized medicine. *J Transl Med* 2011; **9**: 119 [PMID: 21781349 DOI: 10.1186/1479-5876-9-119]
 - 32 **Lei Z, Tan IB, Das K, Deng N, Zouridis H, Pattison S, Chua C, Feng Z, Guan YK, Ooi CH, Ivanova T, Zhang S, Lee M, Wu J, Ngo A, Manesh S, Tan E, Teh BT, So JB, Goh LK, Boussioutas A, Lim TK, Flotow H, Tan P, Rozen SG.** Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil. *Gastroenterology* 2013; **145**: 554-565 [PMID: 23684942 DOI: 10.1053/j.gastro.2013.05.010]
 - 33 **Abe H, Maeda D, Hino R, Otake Y, Isogai M, Ushiku AS, Matsusaka K, Kunita A, Ushiku T, Uozaki H, Tateishi Y, Hishima T, Iwasaki Y, Ishikawa S, Fukayama M.** ARID1A expression loss in gastric cancer: pathway-dependent roles with and without Epstein-Barr virus infection and microsatellite instability. *Virchows Arch* 2012; **461**: 367-377 [PMID: 22484628 DOI: 10.1038/ng.2246]

- 22915242 DOI: 10.1007/s00428-012-1303-2]
- 34 **Nagarajan N**, Bertrand D, Hillmer AM, Zang ZJ, Yao F, Jacques PE, Teo AS, Cutcutache I, Zhang Z, Lee WH, Sia YY, Gao S, Ariyaratne PN, Ho A, Woo XY, Veeravali L, Ong CK, Deng N, Desai KV, Khor CC, Hibberd ML, Shahab A, Rao J, Wu M, Teh M, Zhu F, Chin SY, Pang B, So JB, Bourque G, Soong R, Sung WK, Tean Teh B, Rozen S, Ruan X, Yeoh KG, Tan PB, Ruan Y. Whole-genome reconstruction and mutational signatures in gastric cancer. *Genome Biol* 2012; **13**: R115 [PMID: 23237666 DOI: 10.1186/gb-2012-13-12-r115]
 - 35 **Deng N**, Goh LK, Wang H, Das K, Tao J, Tan IB, Zhang S, Lee M, Wu J, Lim KH, Lei Z, Goh G, Lim QY, Tan AL, Sin Poh DY, Riahi S, Bell S, Shi MM, Linnartz R, Zhu F, Yeoh KG, Toh HC, Yong WP, Cheong HC, Rha SY, Boussioutas A, Grabsch H, Rozen S, Tan P. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. *Gut* 2012; **61**: 673-684 [PMID: 22315472 DOI: 10.1136/gutjnl-2011-301839]
 - 36 **Melo SA**, Esteller M. Dysregulation of microRNAs in cancer: playing with fire. *FEBS Lett* 2011; **585**: 2087-2099 [PMID: 20708002 DOI: 10.1016/j.febslet.2010.08.009]
 - 37 **Cortez MA**, Bueso-Ramos C, Ferdin J, Lopez-Berestein G, Sood AK, Calin GA. MicroRNAs in body fluids--the mix of hormones and biomarkers. *Nat Rev Clin Oncol* 2011; **8**: 467-477 [PMID: 21647195 DOI: 10.1038/nrclinonc.2011.76]
 - 38 **van Kouwenhove M**, Kedde M, Agami R. MicroRNA regulation by RNA-binding proteins and its implications for cancer. *Nat Rev Cancer* 2011; **11**: 644-656 [PMID: 21822212 DOI: 10.1038/nrc3107]
 - 39 **Lopez-Serra P**, Esteller M. DNA methylation-associated silencing of tumor-suppressor microRNAs in cancer. *Oncogene* 2012; **31**: 1609-1622 [PMID: 21860412 DOI: 10.1038/onc.2011.354]
 - 40 **Mitchell PS**, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Brian KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen BS, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci USA* 2008; **105**: 10513-10518 [PMID: 18663219 DOI: 10.1073/pnas.0804549105]
 - 41 **Ueda T**, Volinia S, Okumura H, Shimizu M, Taccioli C, Rossi S, Alder H, Liu CG, Que N, Yasui W, Yoshida K, Sasaki H, Nomura S, Seto Y, Kaminishi M, Calin GA, Croce CM. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncol* 2010; **11**: 136-146 [PMID: 20022810 DOI: 10.1016/S1470-2045(09)70343-2]
 - 42 **Tong F**, Cao P, Yin Y, Xia S, Lai R, Liu S. MicroRNAs in gastric cancer: from benchtop to bedside. *Dig Dis Sci* 2014; **59**: 24-30 [PMID: 24114043]
 - 43 **Pan HW**, Li SC, Tsai KW. MicroRNA dysregulation in gastric cancer. *Curr Pharm Des* 2013; **19**: 1273-1284 [PMID: 23092346 DOI: 10.2174/138161213804805621]
 - 44 **Albulescu R**, Neagu M, Albulescu L, Tanase C. Tissue and soluble miRNAs for diagnostic and therapy improvement in digestive tract cancers. *Expert Rev Mol Diagn* 2011; **11**: 101-120 [PMID: 21171925 DOI: 10.1586/erm.10.106]
 - 45 **Li SC**, Liao YL, Ho MR, Tsai KW, Lai CH, Lin WC. miRNA arm selection and isomiR distribution in gastric cancer. *BMC Genomics* 2012; **13** Suppl 1: S13 [PMID: 22369582 DOI: 10.1186/1471-2164-13-S1-S13]
 - 46 **Kim YH**, Liang H, Liu X, Lee JS, Cho JY, Cheong JH, Kim H, Li M, Downey TJ, Dyer MD, Sun Y, Sun J, Beasley EM, Chung HC, Noh SH, Weinstein JN, Liu CG, Powis G. AMPK α modulation in cancer progression: multilayer integrative analysis of the whole transcriptome in Asian gastric cancer. *Cancer Res* 2012; **72**: 2512-2521 [PMID: 22434430 DOI: 10.1158/0008-5472.CAN-11-3870]
 - 47 **Azad N**, Zahnow CA, Rudin CM, Baylin SB. The future of epigenetic therapy in solid tumours--lessons from the past. *Nat Rev Clin Oncol* 2013; **10**: 256-266 [PMID: 23546521 DOI: 10.1038/nrclinonc.2013.42]
 - 48 **Zouridis H**, Deng N, Ivanova T, Zhu Y, Wong B, Huang D, Wu YH, Wu Y, Tan IB, Liem N, Gopalakrishnan V, Luo Q, Wu J, Lee M, Yong WP, Goh LK, Teh BT, Rozen S, Tan P. Methylation subtypes and large-scale epigenetic alterations in gastric cancer. *Sci Transl Med* 2012; **4**: 156ra140 [PMID: 23076357 DOI: 10.1126/scitranslmed.3004504]
 - 49 **Gigek CO**, Chen ES, Calcagno DQ, Wisniewski F, Burbano RR, Smith MA. Epigenetic mechanisms in gastric cancer. *Epigenomics* 2012; **4**: 279-294 [PMID: 22690664 DOI: 10.2217/epi.12.22]
 - 50 **Qu Y**, Dang S, Hou P. Gene methylation in gastric cancer. *Clin Chim Acta* 2013; **424**: 53-65 [PMID: 23669186 DOI: 10.1016/j.cca.2013.05.002]
 - 51 **Calcagno DQ**, Gigek CO, Chen ES, Burbano RR, Smith Mde A. DNA and histone methylation in gastric carcinogenesis. *World J Gastroenterol* 2013; **19**: 1182-1192 [PMID: 23482412 DOI: 10.3748/wjg.v19.i8.1182]
 - 52 **Otani K**, Li X, Arakawa T, Chan FK, Yu J. Epigenetic-mediated tumor suppressor genes as diagnostic or prognostic biomarkers in gastric cancer. *Expert Rev Mol Diagn* 2013; **13**: 445-455 [PMID: 23782252 DOI: 10.1586/erm.13.32]
 - 53 **Takamaru H**, Yamamoto E, Suzuki H, Nojima M, Maruyama R, Yamano HO, Yoshikawa K, Kimura T, Harada T, Ashida M, Suzuki R, Yamamoto H, Kai M, Tokino T, Sugai T, Imai K, Toyota M, Shinomura Y. Aberrant methylation of RASGRF1 is associated with an epigenetic field defect and increased risk of gastric cancer. *Cancer Prev Res (Phila)* 2012; **5**: 1203-1212 [PMID: 22961779 DOI: 10.1158/1940-6207.CAPR-12-0056]
 - 54 **Suzuki H**, Yamamoto E, Nojima M, Kai M, Yamano HO, Yoshikawa K, Kimura T, Kudo T, Harada E, Sugai T, Takamaru H, Niinuma T, Maruyama R, Yamamoto H, Tokino T, Imai K, Toyota M, Shinomura Y. Methylation-associated silencing of microRNA-34b/c in gastric cancer and its involvement in an epigenetic field defect. *Carcinogenesis* 2010; **31**: 2066-2073 [PMID: 20924086 DOI: 10.1093/carcin/bgq203]
 - 55 **Suzuki R**, Yamamoto E, Nojima M, Maruyama R, Yamano HO, Yoshikawa K, Kimura T, Harada T, Ashida M, Niinuma T, Sato A, Noshio K, Yamamoto H, Kai M, Sugai T, Imai K, Suzuki H, Shinomura Y. Aberrant methylation of microRNA-34b/c is a predictive marker of metachronous gastric cancer risk. *J Gastroenterol* 2013 Aug 13; Epub ahead of print [PMID: 23942619]
 - 56 **Watanabe Y**, Kim HS, Castoro RJ, Chung W, Estecio MR, Kondo K, Guo Y, Ahmed SS, Toyota M, Itoh F, Suk KT, Cho MY, Shen L, Jelinek J, Issa JP. Sensitive and specific detection of early gastric cancer with DNA methylation analysis of gastric washes. *Gastroenterology* 2009; **136**: 2149-2158 [PMID: 19375421 DOI: 10.1053/j.gastro.2009.02.085]
 - 57 **Oishi Y**, Watanabe Y, Yoshida Y, Sato Y, Hiraishi T, Oikawa R, Maehata T, Suzuki H, Toyota M, Niwa H, Suzuki M, Itoh F. Hypermethylation of Sox17 gene is useful as a molecular diagnostic application in early gastric cancer. *Tumour Biol* 2012; **33**: 383-393 [PMID: 22161215 DOI: 10.1007/s13277-011-0278-y]
 - 58 **Baba S**, Oishi Y, Watanabe Y, Oikawa R, Morita R, Yoshida Y, Hiraishi T, Maehata T, Nagase Y, Fukuda Y, Nakazawa M, Ishigouka S, Hattori N, Suzuki H, Toyota M, Niwa H, Suzuki M, Itoh F. Gastric wash-based molecular testing for antibiotic resistance in *Helicobacter pylori*. *Digestion* 2011; **84**: 299-305 [PMID: 22057261 DOI: 10.1159/000332570]
 - 59 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or

- gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]
- 60 **de Mello RA**, Marques AM, Araújo A. HER2 therapies and gastric cancer: a step forward. *World J Gastroenterol* 2013; **19**: 6165-6169 [PMID: 24115812]
- 61 **Meric-Bernstam F**, Mills GB. Overcoming implementation challenges of personalized cancer therapy. *Nat Rev Clin Oncol* 2012; **9**: 542-548 [PMID: 22850751 DOI: 10.1038/nrclinonc.2012.127]
- 62 **Ohtsu A**, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976 [PMID: 21844504 DOI: 10.1200/JCO.2011.36.2236]
- 63 **Van Cutsem E**, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, Peng Yong W, Langer B, Delmar P, Scherer SJ, Shah MA. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012; **30**: 2119-2127 [PMID: 22565005 DOI: 10.1200/JCO.2011.39.9824]
- 64 **Fuchs CS**, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Taberero J. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**: 31-39 [PMID: 24094768 DOI: 10.1016/S0140-6736(13)61719-5]
- 65 **Matsubara J**, Yamada Y, Hirashima Y, Takahari D, Okita NT, Kato K, Hamaguchi T, Shirao K, Shimada Y, Shimoda T. Impact of insulin-like growth factor type 1 receptor, epidermal growth factor receptor, and HER2 expressions on outcomes of patients with gastric cancer. *Clin Cancer Res* 2008; **14**: 3022-3029 [PMID: 18483367 DOI: 10.1158/1078-0432.CCR-07-1898]
- 66 **Adachi Y**, Li R, Yamamoto H, Min Y, Piao W, Wang Y, Imsumran A, Li H, Arimura Y, Lee CT, Imai K, Carbone DP, Shinomura Y. Insulin-like growth factor-I receptor blockade reduces the invasiveness of gastrointestinal cancers via blocking production of matrilysin. *Carcinogenesis* 2009; **30**: 1305-1313 [PMID: 19493905 DOI: 10.1093/carcin/bgp134]
- 67 **Adachi Y**, Yamamoto H, Ohashi H, Endo T, Carbone DP, Imai K, Shinomura Y. A candidate targeting molecule of insulin-like growth factor-I receptor for gastrointestinal cancers. *World J Gastroenterol* 2010; **16**: 5779-5789 [PMID: 21154998 DOI: 10.3748/wjg.v16.i46.5779]
- 68 **Popa EC**, Shah MA. Met, IGF1R, and other new targets in upper GI malignancies. *Curr Treat Options Oncol* 2013; **14**: 321-336 [PMID: 23873272 DOI: 10.1007/s11864-013-0245-5]
- 69 **Singh P**, Alex JM, Bast F. Insulin receptor (IR) and insulin-like growth factor receptor 1 (IGF-1R) signaling systems: novel treatment strategies for cancer. *Med Oncol* 2014; **31**: 805 [PMID: 24338270 DOI: 10.1007/s12032-013-0805-3]
- 70 **Li H**, Adachi Y, Yamamoto H, Min Y, Ohashi H, Ii M, Arimura Y, Endo T, Lee CT, Carbone DP, Imai K, Shinomura Y. Insulin-like growth factor-I receptor blockade reduces tumor angiogenesis and enhances the effects of bevacizumab for a human gastric cancer cell line, MKN45. *Cancer* 2011; **117**: 3135-3147 [PMID: 21264842 DOI: 10.1002/cncr.25893]
- 71 **Zhao X**, Dou W, He L, Liang S, Tie J, Liu C, Li T, Lu Y, Mo P, Shi Y, Wu K, Nie Y, Fan D. MicroRNA-7 functions as an anti-metastatic microRNA in gastric cancer by targeting insulin-like growth factor-1 receptor. *Oncogene* 2013; **32**: 1363-1372 [PMID: 22614005 DOI: 10.1038/onc.2012.156]

P- Reviewers: Deng SL, Reim D, Sperti C S- Editor: Qi Y
L- Editor: A E- Editor: Ma S





Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1007-9327



Effect of graft sources on allogeneic hematopoietic stem cell transplantation outcome in adults with chronic myeloid leukemia in the era of tyrosine kinase inhibitors: a Japanese Society of Hematopoietic Cell Transplantation retrospective analysis

Kazuteru Ohashi · Tokiko Nagamura-Inoue · Fumitaka Nagamura · Arinobu Tojo · Kouichi Miyamura · Takehiko Mori · Mineo Kurokawa · Shuichi Taniguchi · Jun Ishikawa · Yasuo Morishima · Yoshiko Atsuta · Hisashi Sakamaki

Received: 19 October 2013 / Revised: 1 July 2014 / Accepted: 2 July 2014 / Published online: 2 August 2014
© The Japanese Society of Hematology 2014

Abstract We retrospectively compared transplant outcomes for related bone marrow transplantation (rBMT), related peripheral blood stem cell transplantation (rPBSCT), unrelated bone marrow transplantation (uBMT), and unrelated cord blood transplantation (CBT) in 1,062 patients with chronic myeloid leukemia (CML) aged 20 years or over between January 1, 2000 and December 31, 2009 in Japan. The disease status was as follows: chronic phase 1 (CP1, $n = 531$), CP 2 or later including accelerated phase (CP2-AP, $n = 342$) and blastic crisis

(BC, $n = 189$). Graft sources (GS) were rBMT ($n = 205$), uBMT ($n = 507$), rPBSCT ($n = 226$) or CBT ($n = 124$). In multivariate analysis in CP1, lower overall survival (OS) (relative risk [RR]: 6.01, 95 % confidence interval [CI]: 1.20–29.97, $P = 0.029$) and leukemia-free survival (LFS) (RR: 4.26, 95 % CI: 1.24–14.62, $P = 0.021$) were observed in uBMT compared with those in rBMT. For patients in the advanced phase of CML beyond CP1, GS had no significant impact on OS or LFS. Our results support the use of rBMT for adults with CML in CP1, but in contrast to previous reports, the superiority of rPBSCT in advanced stage of CML was not confirmed in our cohorts.

On behalf of Choric Myeloid Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation.

Electronic supplementary material The online version of this article (doi:10.1007/s12185-014-1632-9) contains supplementary material, which is available to authorized users.

Keywords Chronic myeloid leukemia · Allogeneic hematopoietic stem cell transplantation · Graft sources

K. Ohashi (✉) · H. Sakamaki
Hematology Division, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan
e-mail: k.ohashi@cick.jp

K. Miyamura
Department of Hematology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan

T. Nagamura-Inoue
Department of Cell Processing and Transfusion, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

T. Mori
Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

T. Nagamura-Inoue
Japan Cord Blood Bank Network, Tokyo, Japan

M. Kurokawa
Department of Cell Therapy and Transplantation Medicine, The University of Tokyo, Tokyo, Japan

F. Nagamura
Division of Clinical Trial Safety Management, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

S. Taniguchi
Department of Hematology, Toranomon Hospital, Tokyo, Japan

A. Tojo
Department of Hematology/Oncology, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

J. Ishikawa
Department of Hematology and Chemotherapy, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Y. Morishima
Division of Epidemiology/Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan