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Molecular medicine of gastric adenocarcinomas

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Upper gastrointestinal (GI) tract malignancies, including carcinomas of the esophagus, the GI junction and the stomach, are among the most common cancers worldwide. Overall survival is poor because many patients present with locally advanced and often incurable disease. This review focuses on the pathogenesis of adenocarcinomas of the stomach. It summarises recent findings on genetic predisposition to gastric cancer, in particular in relation to germline mutations in the E-cadherin gene. It also describes the molecular basis of sporadic gastric cancer, including alterations in oncogenes, tumour suppressor genes and growth factors, and discusses how these findings might be used in the clinic for improved diagnosis and therapy.

According to Laurén's classification, gastric adenocarcinoma can be divided into two major histologically distinct types – intestinal and diffuse – each of which accounts for half of the cases (Ref. 1). Intestinal-type carcinomas have a glandular pattern and are usually accompanied by papillary or tubular formation or solid components, and predominate in patients from certain geographical areas. By contrast, the diffuse type consists of poorly cohesive cells diffusely infiltrating the gastric wall with little or no gland formation, and is associated with a worse prognosis. A special subgroup of this type is the so-called signet-ring cell carcinoma in which a classical signet-ring appearance is formed owing to the cell nucleus being pushed against the cell membrane, creating an expanded, globoid, optically clear cytoplasm (Ref. 2).

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Gastric cancer spreads by metastasis or peritoneal dissemination. Early gastric cancer (i.e. a carcinoma that is limited to the mucosa or submucosa) has a low incidence of vessel invasion and lymph-node metastasis. About 95% of patients with early gastric cancer survive 5 years after surgery. Patients with advanced gastric cancer have a 5-year survival rate of 10–30%, depending on the depth of invasion. Unfortunately, most patients with advanced carcinoma already have lymph-node metastases at the time of diagnosis and therefore a poor survival rate.

Genetic predisposition

Dietary habits and environmental factors, especially salt intake and bacterial infection with *Helicobacter pylori* (Ref. 3), have been considered as major risk factors for the development of gastric carcinoma. Certain precursor conditions are also associated with an increased risk, including chronic atrophic gastritis, pernicious anaemia and gastric adenomatous polyps (Refs 3, 4). In addition, there is increasing evidence that genetic predisposition, in at least a subset of gastric cancer patients, also plays an important role.

In epidemiological studies, a familial clustering of gastric cancer was found in 10% of cases (Ref. 5), and 1–3% of gastric carcinomas are considered to be related to a hereditary gastric cancer predisposition syndrome (Ref. 6). As discussed below, a molecular genetic basis has been described for this specific hereditary gastric cancer syndrome, which is characterised by the occurrence of diffuse-type gastric carcinoma (Ref. 7). In addition, gastric carcinoma is observed more frequently in association with hereditary tumour syndromes, which are mainly characterised by the occurrence of carcinomas in other organs (Table 1). Furthermore, certain DNA polymorphisms in pro-inflammatory genes are associated with an increased risk for gastric cancer in individuals infected with *H. pylori*, thus providing a link between an environmental condition and specific host genetic factors (Refs 8, 9).

Hereditary diffuse-type gastric cancer syndrome (HDGC)

Germline mutations in the *CDH1* gene, encoding E-cadherin, were first described as the molecular genetic cause for a hereditary gastric cancer syndrome in three Maori families (Ref. 7). E-cadherin is a calcium-dependent cell adhesion molecule whose intact function is crucial for the establishment and maintenance of epithelial tissue polarity and structural integrity. To date, inactivating germline mutations of the gene have been reported in at least 36 gastric cancer families of various ethnic origins (Refs 7, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20). In addition, several missense mutations have been described, and functional analysis of selected variants points to a potential pathogenic role at least for some of them (Ref. 21). Gastric carcinoma arising in the context of germline mutations in E-cadherin is typically of the diffuse type. As somatic E-cadherin mutations frequently occur in sporadic gastric cancer of the diffuse type as well as in sporadic lobular breast carcinomas (Refs 22, 23), the occurrence of lobular breast carcinomas in association with E-cadherin germline mutations have also been described in several families (Refs 12, 13, 18, 24).

On the basis of the limited data to date, the penetrance of gastric cancer by the age of 80 for E-cadherin germline mutation carriers has been calculated to be 67% for men and 83% for women, compared with 39% for women with respect to breast cancer (Ref. 24). Guidelines for genetic counselling and testing for germline mutations in E-cadherin have been developed by the International Gastric Cancer Linkage Consortium (Ref. 25), which recommends testing of patients with diffuse-type gastric cancer who have: (1) at least one family member with histopathologically verified diffuse-type gastric cancer diagnosed before the age of 50; or (2) two family members with histopathological confirmation of the disease diagnosed at any age (Ref. 25). Using these criteria, the incidence of E-cadherin germline mutations in HDGC has been assumed to be 25–40% in this group of patients (Refs 21, 25). If histopathological confirmation is available only for the index patient, but not for the affected relatives, gastric cancer arising in this context is called familial gastric cancer, and a lower incidence of germline mutations in E-cadherin of around 8% is found in this group of patients (Refs 18, 19). Testing for germline mutations should be performed only in the context of thorough genetic counselling. The identification of a germline mutation in E-cadherin in a patient opens the possibility of testing asymptomatic at-risk members of the respective family. These individuals would need to be included in an intensive cancer-screening program, and the option of prophylactic gastrectomy might be considered.

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Table 1. Overview of gastric cancer in hereditary tumour syndromes

Syndrome	Defective genes	Chromosomes	Main tumours	Associated tumours	Refs
HDGC (hereditary diffuse-type gastric cancer syndrome)	*E-cadherin*	16q22	Diffuse-type gastric carcinoma	Lobular breast carcinoma, and colon carcinoma	7, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
HNPCC (hereditary nonpolyposis colorectal cancer syndrome)	*hMLH1* *hMSH2* *hMSH6* *hPMS2*	3p21 2p16 2p16 7p22	Colon carcinoma	Endometrial, gastric, small-bowel and urothelial carcinomas	26, 27, 28
Li–Fraumeni syndrome	*p53*	17p13	Breast carcinoma, osteosarcoma, brain tumours, and soft-tissue sarcoma	Gastric and colon carcinomas, adrenocortical carcinomas, haematological and gynaecological malignancies	18, 19, 30, 31, 32
FAP (familial adenomatous polyposis coli)	*APC*	5q21	Numerous colon adenomas and carcinomas	Fundic gland polyps, gastric adenomas and carcinoma, papillary thryoid tumours, desmoid tumours, medulloblastoma and hepatoblastoma	33, 34
Peutz–Jeghers syndrome	*STK11*	19p13	Hamartomatous polyps in the small intestine, and occasionally in the colon and stomach	Gastrointestinal carcinomas, and breast, testicular and ovarian carcinomas	35, 36
Juvenile polyposis	*DPC4/SMAD4* *PTEN* *BMPR1A*	18q21 10q23 10q22-23	Hamartomatous polyps in the colon, and occasionally in the stomach and small bowel	Gastrointestinal carcinomas	37, 38, 39, 40

Abbreviations: *APC*, adenomatous polyposis coli; *BMPR1A*, bone morphogenetic protein receptor type IA precursor; *DPC4/SMAD4*, deleted in pancreatic carcinoma 4/SMA- and MAD-related protein 4 (also known as MADH4); *hMLH1*, human mutL homologue 1; *hMSH2*, human mutS homologue 2; *hMSH6*, human mutS homologue 6; *hPMS2*, human postmeiotic segregation increased 2; *PTEN*, phosphatase and tensin homologue; *STK11*, serine/threonine kinase 11.

Gastric cancer in association with hereditary tumour syndromes

The HNPCC syndrome (hereditary nonpolyposis colorectal cancer syndrome) is an autosomal-dominant, inherited tumour-predisposition syndrome that is primarily characterised by the familial occurrence of colorectal carcinoma. However, extracolonic carcinomas of the endometrium, ureter, duodenum and stomach are observed significantly more frequently in HNPCC families (Refs 26, 27). Germline mutations in DNA mismatch repair genes are the molecular genetic cause of the syndrome in the majority of families (Ref. 27). Tumours of HNPCC patients typically

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show a high degree of microsatellite instability (MSI-H), which reflects numerous replication errors that are normally corrected by an intact DNA mismatch repair system. Gastric carcinomas that are associated with HNPCC are typically MSI-H and, histopathologically, are mostly of the intestinal type (Ref. 28).

The Li–Fraumeni syndrome is a rare inherited cancer syndrome that results from germline mutations of the *p53* tumour suppressor gene (Ref. 29). Breast carcinoma is the most frequently observed tumour type, followed by osteosarcoma, brain tumours and soft-tissue sarcomas. Tumours of the GI tract account for 7% of all neoplasms in this syndrome. Among these, gastric carcinoma (57%) is more frequent than colon carcinoma (31%) (Ref. 30). Some families harbouring a germline *p53* mutation show a prevalence of, or an exclusive occurrence of, gastric carcinomas, indicating that genetic screening of *p53* should be considered if no germline mutation in the E-cadherin gene is found (Refs 18, 19, 31, 32).

Several other familial polyposis syndromes have been described in which affected individuals present with gastric carcinoma. Besides the occurrence of hundreds of adenomas in the colon, patients with familial adenomatosis polyposis coli frequently develop multiple polyps in the stomach and duodenum and have an increased risk of developing a carcinoma (Refs 33, 34).

An increased risk for gastric cancer is also known for patients with the Peutz–Jeghers syndrome, which is a rare, autosomal-dominant inherited disease characterised by a GI hamartomatous polyposis, and mucocutaneous pigmentation of the lips, buccal mucosa and digits (Refs 35, 36). Familial juvenile polyposis is another autosomal-dominant inherited condition in which affected individuals develop hamartomatous polyps preferentially in the colon, but also occasionally in the small bowel and the stomach (Refs 37, 38). Although neoplastic transformation occurs infrequently, the affected patients have an increased risk of many types of cancer including those of the GI tract (Refs 37, 38, 39, 40).

Increased gastric cancer risk in association with DNA polymorphisms

An association of naturally occurring DNA polymorphisms in the interleukin 1 (IL-1) gene cluster with a response to *H. pylori* infection and an increased risk for sporadic gastric cancer has been demonstrated (Ref 8, 9). It is thought that these polymorphisms enhance the production of the pro-inflammatory cytokine IL-1β and inhibit gastric acid secretion, leading to hypochlorhydria (an abnormally low amount of stomach HCl) and gastric atrophy, which are possible precursors of gastric carcinoma. These findings thus provide a very interesting link between an environmental condition and specific host genetic factors.

Molecular basis

Many studies in the past decade have clearly demonstrated that multiple genetic alterations – including changes in so-called tumour suppressor genes and oncogenes – are responsible for the development and progression of gastric cancer. Alterations have been identified in specific genes that play important roles in diverse cellular functions such as cell adhesion, signal transduction, differentiation, development, gene transcription or DNA repair. What must now be confirmed in more detail is at which stage the genetic abnormalities take place and how they could be used for more-specific diagnosis and more-selective therapy of the disease.

Dysregulation of gastric cell proliferation and differentiation might be provoked by any one of a number of catalogued gene alterations. Such tumour-associated gene alterations have frequently been reported in both histological subtypes of gastric cancer. Figure 1 provides a summary of known genetic alterations in gastric cancer, some of which are discussed below in more detail. The combination of molecular changes differs between intestinal- and diffuse-type tumours, as recently demonstrated by cDNA microarray analysis, suggesting that they might have unique genetic pathways (Refs 41, 42, 43). Further studies using cDNA microarrays for gastric cancer profiling have reported characteristic gene expression patterns for chronic gastritis, intestinal metaplasia, intestinal gastric cancer and diffuse gastric cancer (Refs 44, 45). Some of these genes might play important roles in gastric tumour progression and could be immediately useful for prognosis and treatment stratification.

Microsatellite instability

Genetic instability in cancers can be classified into two major types: chromosomal instability (CIN) and microsatellite instability (MSI). Tumours of the CIN phenotype are characterised by a high frequency of allelic losses, and mutations in tumour suppressor genes and oncogenes. MSI is

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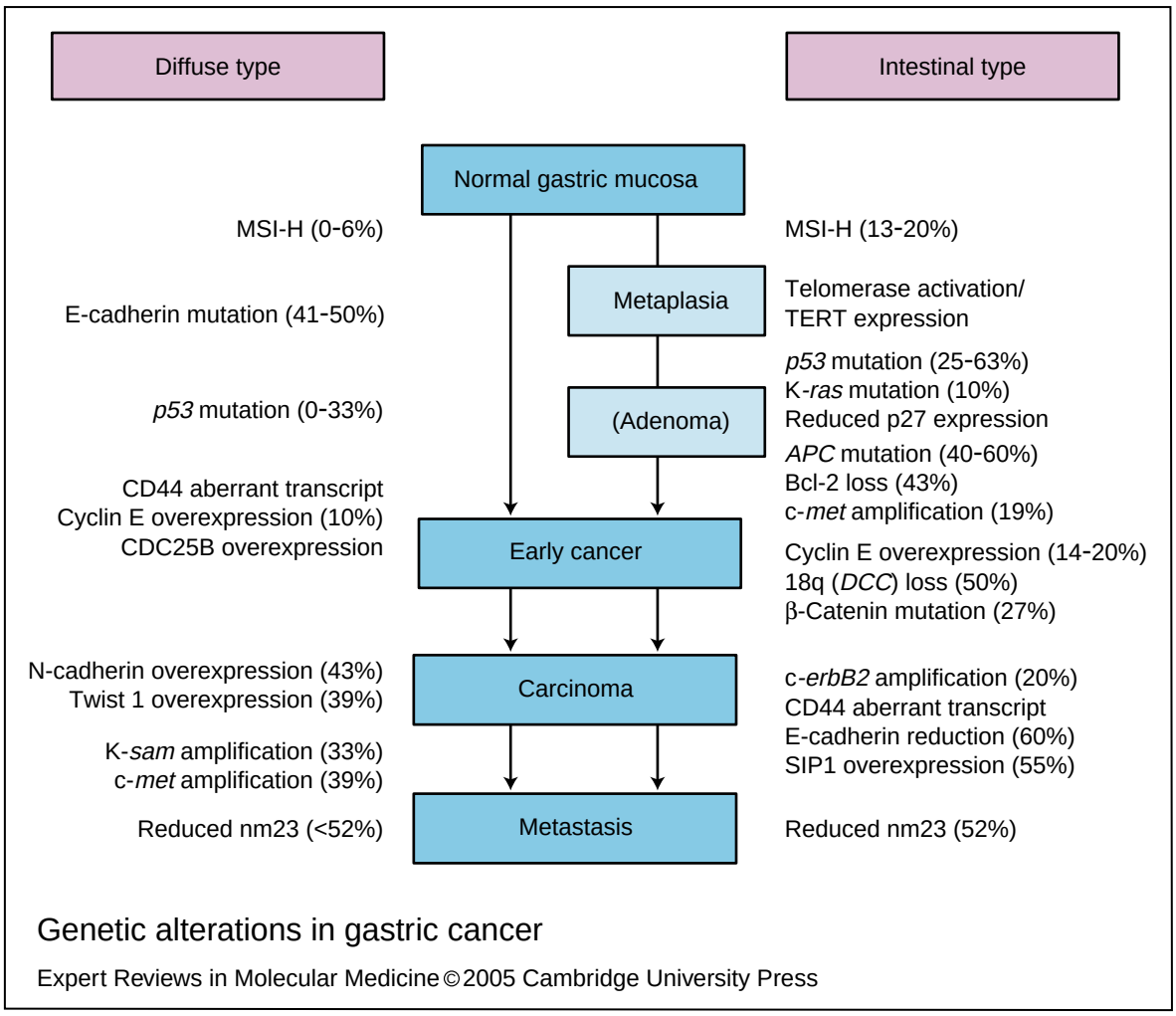

Figure 1. Genetic alterations in gastric cancer. The molecular changes differ between the two major types of gastric cancer: intestinal- and diffuse-type tumours. The alterations, such as mutation, overexpression or amplification, are ordered according to the stage of cancer development. Molecular changes in specific genes involved in cell adhesion, signal transduction, differentiation, development, gene transcription, and DNA repair have been identified. The percentages in parenthesis indicate the frequencies of the alterations observed when known. Abbreviations: *APC*, adenomatous polyposis coli; Bcl-2, B-cell CLL/lymphoma 2; CD44, CD44 antigen; CDC25B, cell division cycle 25B; c-*erbB2*, v-*erb-b2* erythroblastic leukaemia viral oncogene homologue 2; c-*met*, *met* proto-oncogene (hepatocyte growth factor receptor); *DCC*, deleted in colon cancer; K-*ras*, v-Ki-*ras2* Kirsten rat sarcoma viral oncogene homologue; K-*sam*, encodes fibroblast growth factor receptor 2; MSI-H, microsatellite instability-high; nm23, nonmetastatic cells 1 (protein, NM23, expressed in); p53, tumour protein p53 (Li–Fraumeni syndrome); SIP1, SMAD-interacting protein 1; TERT, telomerase reverse transcriptase; TWIST 1, twist homologue 1.

categorised into two groups: a high frequency MSI (MSI-H), where at least 30% of microsatellite markers are mutated; and a low frequeny of MSI (MSI-L), where less than 30% of the markers are altered. The MSI-H phenotype reflects defects of the DNA mismatch repair system, whereas the biological background of MSI-L is poorly understood. MSI-H is detected in 2–22% of gastric carcinomas (Refs 46, 47, 48). Tumours that show such instability tend to be intestinal-type cancers. Loss of either hMLH1 or hMSH2 mismatch repair proteins affects almost all MSI-H cases, suggesting inactivation of both alleles, possibly by hypermethylation. For instance, a significant correlation has been found between methylation of hMLH1 and a high level of MSI-H: methylation of

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hMLH1 was present in 71% of MSI-H tumours, but only 8% of MSI-L tumours and 13% of microsatellite-stable tumours. The authors concluded that hMLH1 promoter methylation is an early and frequent event in gastric tumourigenesis (Ref. 49).The frequency of MSI-L, which is strongly dependent on the number of analysed microsatellite loci, showed a considerable variation in gastric cancer; it is found in 8–20% of gastric tumours analysed by 6–8 microsatellite markers (Refs 46, 47, 48).

Tumour suppressor genes and cell adhesion molecules

Inactivation as a result of loss of heterozygosity (LOH) and/or mutation of the genes encoding p53, APC (the gene defective in adenomatous polyposis coli) and DCC (for 'deleted in colon cancer') have been reported in gastric cancer. Mutation/LOH of the *p53* locus was detected in about 30% of gastric cancers independently of the histological subtype. However, it should be emphasised that *p53* mutation reports are not consistent in the literature. This is at least in part due to the techniques used for mutation detection. Such techniques include immunohistochemistry, PCR single-strand conformation polymorphism analysis, denaturing high-pressure liquid chromatography (DHPLC) and sequencing. Therefore, no clear picture has emerged with regard to *p53* mutations in gastric cancer.

Up to 60% of the intestinal-type tumours and approximately 25% of adenomas have a mutation/LOH of the *APC* gene (Refs 29, 50, 51). These alterations are rare in diffuse-type tumours but may be associated with signet-ring cell carcinomas. The *APC* gene product binds to the multifunctional protein β-catenin, whose free concentration within the cell is strictly regulated and kept at a low level (Ref. 52). In the case of *APC* alterations or β-catenin mutations, the amount of free β-catenin is elevated. After interaction with the transcription factor lymphoid enhancer-binding factor 1 (LEF-1), β-catenin translocates into the nucleus where it modulates gene expression (Ref. 53). β-catenin mutations have been detected at a variable frequency in gastric carcinomas (Refs 54, 55, 56). Both APC and β-catenin are members of the so-called Wnt/wingless signal transduction pathway that is altered in over 90% of colon cancers and is currently being intensively analysed in order to find small molecules for selectively interfering with its activation in tumour cells.

E-cadherin is another binding partner of β-catenin and plays a crucial role in establishing the structural integrity of epithelial tissues (Refs 57, 58). E-cadherin mutations have been detected in 50% of diffuse-type tumours (Refs 22, 23). However, E-cadherin mutations are absent in intestinal-type tumours. Interestingly, in contrast to the germline gene mutations mentioned above, somatic E-cadherin mutations are typically either in-frame deletions removing partial or complete sequences from the mRNA or are point mutations resulting in single amino acid changes. The high correlation between mutations in a specific gene and the histological subtype of a tumour is exceptional. Because of its tumour specificity and its biological relevance for malignancy, mutant E-cadherin is an excellent marker for diagnosis and a very attractive target for novel therapeutic interventions (see below). However, in many cases, E-cadherin immunoreactivity is absent, either because of promoter hypermethylation (Refs 59, 60) or direct transcriptional inactivation by repressor molecules (Refs 61, 62, 63). One direct E-cadherin transcriptional repressor is Snail, a zinc finger transcription factor that plays a major role during a process called epithelial mesenchymal transition (EMT) (Ref. 64). EMT involves loss of E-cadherin, cell–cell dissociation, cell migration and invasion. Using real-time reverse transcription PCR, Snail mRNA expression was demonstrated in 11/28 (39%) gastric cancers, exclusively in the diffuse type (Ref. 65).

Tyrosine kinase receptors

The *met* proto-oncogene encodes the hepatocyte growth factor receptor, which is preferentially amplified and overexpressed in diffuse-type tumours (Ref. 66). Amplification of *met* correlates with stage and prognosis. Other growth factor and receptor signal systems that may be altered include epidermal growth factor (EGF), tumour growth factor α and K-Sam. The K-*sam* gene was first described as an amplified gene from the gastric cancer cell line KATOIII (Ref. 92); its product is identical to fibroblast growth factor receptor 2. The oncogene product ErbB2, a 185 kDa glycoprotein with tyrosine kinase activity and homology to the EGF receptor (EGF-R), is amplified in approximately 20% of intestinal-type gastric carcinomas, and overexpression is associated with a poor prognosis (Ref. 67). In addition, overexpression of EGF-R was shown to be associated with decreased survival (Ref. 68).

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Apoptosis and cell-cycle regulators

Genes that regulate programmed cell death or apoptosis can contribute to the development of cancer. LOH at the *bcl-2* locus (encoding Bcl-2, an apoptosis inhibitor localised at the inner mitochondrial membrane) is associated with intestinal-type tumours (Refs 69, 70). Expression of the SC-1 antigen, an apoptosis receptor, is preferentially seen in diffuse-type tumours (Ref. 71).

The cell cycle is controlled by both positive and negative regulators. Genetic alterations and abnormal expression of various cyclins and cyclin-dependent kinases (CDKs), as well as CDK inhibitors, play a role in gastric cancer pathogenesis (Refs 72, 73, 74). Amplification of cyclin E is seen in 15–20% of gastric cancers (Ref. 72).

Diagnostic and therapeutic implications

It is important to establish methods for: quantification of an individual's risk for developing gastric cancer; tumour diagnosis prior to tumour invasion and dissemination; and monitoring the efficacy of a therapeutic or preventive intervention. Some examples of how tumour-associated gene alterations might be used to develop novel innovative diagnostics and therapeutics are mentioned here.

Chemotherapy-response prediction

Gastric carcinoma is characterised by a high mortality rate, mainly as a result of its late diagnosis at advanced stages. Neoadjuvant chemotherapy has been used since 1989 in several clinical trials to improve prognosis. However, only 30% of patients respond to treatment and the majority undergo an expensive and potentially harmful therapy without benefit (Ref. 75). Thus, the identification of molecular genetic parameters in pre-therapeutic biopsies that could predict response is highly attractive.

Several molecular markers have been investigated as potential response predictors. Fluorouracil (5-FU) is a chemotherapy used for certain types of cancer including carcinomas of the stomach, and its target enzyme is thymidylate synthase (TS) (Ref. 76). TS has been widely studied for an association with response in various tumour types; however, for gastric cancer the results are inconsistent. High TS expression has been found to be associated with no response by some authors (Refs 77, 78), whereas a lack of an association between TS expression and response has been reported by others (Refs 79, 80). An association of TS expression with survival but not with response has been reported, indicating that TS has a more important role for tumour progression than in predicting 5-FU sensitivity (Refs 79, 80).

Dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP) are two other important regulatory enzymes involved in the degradation of 5-FU. Low levels of DPD have been shown to be associated with response in gastric carcinoma (Refs 79, 80), whereas conflicting results have been reported for TP. Interestingly, the combined consideration of TP and GADD45, a cell-cycle regulator thought to be involved in the repair of cisplatin-induced DNA damage, showed the most obvious association with therapy response in a study of 61 gastric cancer biopsies (Ref. 79). Among other genes that have been related to the action of cisplatin, ERCC1, an enzyme involved in nucleotide-excision repair, was found to have a significant association with response in a neoadjuvant therapy regimen based on 5-FU and cisplatin (Ref. 78).

Other potential predictors of therapy response, such as glutathione *S*-transferase, thymidine phosphorylase, vascular endothelial growth factor, and apoptosis-related genes and gene products such as Bcl-2, Bax and p53, have mostly been assessed by immunohistochemistry and the studies have been inconclusive (Refs 77, 81, 82). Mutations of the *p53* gene revealed no association with response or survival, but tumours with a high LOH rate, determined by microsatellite analysis, showed a better response to a cisplatin-based chemotherapy (Ref. 83). Although several of these studies point to promising markers with a potential use in chemotherapy-response prediction, prospective studies for validation are necessary before they can be used in clinical practice.

Prophylactic gastrectomy in HDGC

Owing to the difficulty of detecting diffuse-type gastric cancer by endoscopy, prophylactic gastrectomy has been performed in asymptomatic carriers with germline truncating mutations in E-cadherin. Early diffuse-type gastric cancer seen as microscopic foci of signet-ring cell adenocarcinoma has been found in all prophylactic gastrectomies reported so far and, on the basis of these findings, prophylactic gastrectomy has to be considered for young asymptomatic mutation

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carriers with highly penetrant germline mutations (Refs 84, 85, 86). However, because of the limited number of patients enrolled in the respective studies, data on the survival benefit and on morbidity of prophylactic gastrectomy in E-cadherin germline mutation carriers are still insufficient, and further studies are required to define the optimal therapeutic and surveillance strategies.

PCR-based diagnosis

More than 70% of somatic E-cadherin mutations in diffuse-type gastric cancer are complete or partial deletions of exons (Refs 22, 23), and these characteristic mutations might prove useful for diagnosis. Since no such characteristic gene alterations are found in intestinal-type tumours, we focus on diffuse-type tumours for the further discussion of clinical implications. Detection of nodal metastasis and peritoneal tumour cell dissemination are both of great importance in prognosis and – if not detected – could at least in part explain early recurrence after histopathologically approved curative resection. A rapid (PCR-based) E-cadherin mutation detection technique has been established that allows positive results within a day (Ref. 87). Because of absolute tumour-cell specificity, accuracy in assessing peritoneal tumour spread in gastric cancer could be improved by analysing E-cadherin mutations in addition to conventional cytological analysis of lavage fluids and ascites.

The therapeutic course might be influenced by these or other highly specific molecular approaches. In routine histopathological examination of resection specimens, the likelihood of detecting nodal metastasis is influenced by several factors, including the operative technique, the skill and patience of the pathologist, and the number of sections taken from a paraffin block. In this regard, it would be useful to analyse tumour-specific gene mutation. Mutations in the K-*ras* and *p53* genes have been successfully used to detect micrometastasis in colorectal neoplasms (Refs 88, 89). When molecular analysis is performed using resected tumour tissues or biopsies, tissue heterogeneity has to be considered. This problem could be solved by laser-based microdissection techniques and subsequent genetic analysis of the resultant homogenous cell population.

Immunotherapy

The selective delivery of cytotoxic compounds to tumour cells is an old but attractive concept. The goal is to destroy tumour cells yet leave nontumourous cells unaffected. A novel therapeutic approach to treat gastric cancer using monoclonal antibody (mAb) SC-1 has recently been described (Ref. 71). The human mAb was isolated from a patient with signet-ring cell carcinoma and shown to react with a 50 kDa surface molecule expressed by gastric carcinoma cells. The mAb induces apoptosis and inhibits proliferation of gastric carcinoma cells in vitro, and significantly reduced gastric cancer growth in vivo (Ref. 71). Furthermore, the mAb shows no toxic crossreactivity to other organs or tissues, even if applied in high doses. The concept of tumour-specific apoptosis induction by mAbs may present a novel type of adjuvant cancer therapy.

The mutations detected in the E-cadherin gene typically affect the extracellular portion of the molecule and do not interrupt the translation of the mRNA (in-frame deletions) but will result in the synthesis of a slightly shortened protein. This special type of mutation allows the detection of the altered protein at the cell membrane and the construction of mutation-specific mAbs (Ref. 90). Two E-cadherin-mutation-specific mAbs (E-cad delta 9-1 and E-cad delta 8-1) have been isolated that react exclusively with mutant-E-cadherin-positive diffuse-type gastric cancers, lacking in-frame exon 9 or exon 8, respectively, because of splice-site mutations. Since both mutation-specific mAbs work very well with archival material, they provide an optimal means for routine diagnosis, simply by staining biopsies. Sequencing of the E-cadherin gene is not necessary because the mAbs specifically react with the fusion junction between exon 8 and exon 10 or exon 7 and exon 9. Diagnosing gastric cancer histologically is usually not a problem in routine pathology; however, screening patients for these specific mutations is a prerequisite to identify patients for which a personalised new therapy might be beneficial.

Intraperitoneal tumour cell dissemination, the precursor of a peritoneal carcinomatosis, is a crucial step in the course of solid GI malignancies. Because of peritoneal seeding the progression of the disease is dramatic, and symptoms such as ascites formation and intestinal obstruction result in a substantial deterioration of the quality of life. Thus far, there is no standard therapy for peritoneal tumour spread in solid GI tumours because of severe unspecific side effects. The application of systemic or intraperitoneal chemotherapy and radiation has always been experimental and

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limited in dose; therefore, new therapeutic strategies are urgently needed for this type of cancer. Recently, in order to establish a locoregional radioimmunotherapy, the mutation-specific E-cadherin mAb E-cad delta 9-1 was conjugated to the high-energy alpha-emitter Bi-213 and tested for its binding specificities in subcutanous and intraperitoneal nude mouse models. Initial studies suggest that it will be successful for alpha radioimmunotherapy of desseminated tumours (Ref. 91).

Outlook

Much has been learned about the pathogenesis of gastric cancer, and the first therapeutic molecules are on their way into clinical use. However, translation of the results towards a successful treatment is slow. Germline mutations in the E-cadherin gene have been identified in a gastric cancer family syndrome and are being used to identify asymptomatic mutations carriers for prophylactic gastrectomy. However, further studies are needed to design more optimal therapeutic and surveillance strategies. Since E-cadherin germline mutations are found in only a subset of cases, other genes involved in hereditary diffuse-type gastric cancer have to be identified. For sporadic gastric cancers, alterations in a variety of genes, including cell adhesion molecules and tyrosine kinase receptors, have been identified. These genes were identified by tumour analysis of one gene at a time. In the future, however, novel platform technologies, such as cDNA microarrays, for the molecular analysis of the disease will allow analysis of many genes in one experiment. In addition, protein microarrays will find their way into molecular pathology laboratories for profiling diseased versus non-neoplastic tissues in order to identify novel target molecules.

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Further reading, resources and contacts

E-cadherin in Online Mendelian Inheritance in Man (OMIM):

http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=192090

Gastric cancer in OMIM:

http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=137215

Esophageal cancer in OMIM:

http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=133239

Features associated with this article

Figure
Figure 1. Genetic alterations in gastric cancer.

Table
Table 1. Overview of gastric cancer in hereditary tumour syndromes.

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