GASTRIC CARCINOGENESIS pdf

1: Gastric carcinogenesis

GASTRIC CARCINOMA. Cancer is a major public health problem and at the beginning of the 19th century, gastric cancer was the second most common cancer worldwide[].

This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract The oxygen-derived free radicals that are released from activated neutrophils are one of the cytotoxic factors of Helicobacter pylori-induced gastric mucosal injury. Increased cytidine deaminase activity in H. Cytotoxin-associated gene A CagA is delivered into gastric epithelial cells via bacterial type IV secretion system, and it causes inflammation and activation of oncogenic pathways. Aberrant expression of microRNAs is also reportedly linked to gastric tumorogenesis. Moreover, recent advances in molecular targeting therapies provided a new interesting weapon to treat advanced gastric cancer through anti-human epidermal growth factor receptor 2 HER-2 therapies. This updated review article highlights possible mechanisms of gastric carcinogenesis including H. According to a systemic review of 15 papers, H. A recent meta-analysis of RCTs also shows that H. Bacterial virulence factors, such as, cytotoxin-associated gene A CagA , cause inflammation and activate oncogenic pathways. Activated neutrophils are the main source of reactive oxygen species ROS and reactive nitrogen species production in H. Excessive oxidative stress can damage DNA in gastric epithelial cells, indicating its possible involvement in gastric carcinogenesis [7]. Gastric cancer arises from multiple genetic and epigenetic alterations in oncogenes, tumor-suppressor genes, cell cycle regulators, cell-adhesion molecules, and DNA repair genes. The roles of microRNAs are increasingly apparent, and aberrant expression of microRNAs may contribute to the development and progression of gastric cancer. Moreover, recent advances in molecular therapies provided a new interesting weapon to treat advanced gastric cancer through anti-human epidermal growth factor receptor 2 HER-2 therapies. Consequently, this paper summarizes the molecular mechanism of H. Oxidative Stress Oxygen-derived free radicals that are released from activated neutrophils are considered potential toxic factors that contribute to H. Free radicals, including ROS and reactive nitrogen species, can bind with nucleic acids, turning them into mutated forms that play a role in multistep carcinogenesis [9]. The CD44 variant CD44v , which is a cell-surface marker, that is associated with cancer stem-like cells, interacts with a glutamate-cystine transporter and controls the intracellular level of reduced glutathione GSH [10]. Human gastrointestinal cancer cells with a high level of CD44 expression revealed an enhanced capacity for glutathione synthesis and defense against ROS. These findings indicate that cancer stem-like cells with CD44v expression could have an ROS defense system that results from glutathione synthesis. However, a subpopulation of cells is resistant to apoptosis, despite their high levels of DNA damage. CagA Epidemiological evidence indicates that H. The CagA protein of H. CagA binding to the protooncogene Src homology 2-containing protein tyrosine phosphatase SHP-2 causes aberrant activation of SHP-2 and consequently of the ERK-MAPK mitogen-activated protein kinase pathway, which has been reported to play a role in carcinogenesis by inducing mitogenic responses [14]. These findings are consistent with the fact that East Asian strains dominate in countries with the highest rates of gastric cancer [15]. On the other hand, CagA interacts with many signaling molecules e. CagA, that is translocated into the host cell, is degraded by autophagy and short-lived. However, CagA, that is translocated into CD44v9-positive gastric cancer stem-like cells, which are characterized by ROS resistance that results from their rich GSH content, is thought to escape ROS-dependent autophagy, resulting in gastric carcinogenesis [16]. CagA and major functions. CagA is delivered into gastric epithelial cells via bacterial type IV secretion system. CagA interacts with many signaling molecules that are important for the regulation of cell proliferation, polarity, and motility. AID is specifically induced in germinal center B cells to carry out somatic hypermutation and class-switch recombination, which are two processes that are responsible for antibody diversification. Because of its mutagenic potential, AID expression and activity are tightly regulated to minimize unwanted DNA damage. Surprisingly, AID is also induced by inflammation and microbial infections in nonimmune cells. AID is induced by H. Additionally, AID expression was shown to be triggered by proinflammatory cytokines, such

as TNF- or IL-1, and correlated with mononuclear cell infiltration and intestinal metaplasia. After eradication of H. Strong evidence indicates that CagA-positive H. Whole-exome sequencing revealed that somatic mutations accumulated in various genes in inflamed gastric tissues. The mutations that accumulated in gastric tumors as well as gastric mucosal tissues with H. Epidermal growth factor receptor EGFR , a member of ErbB receptor family, is involved in the regulation of gastric mucosal cell proliferation and progression of gastric cancer. Constitutive activation of Ras and Ras-related proteins promotes cell proliferation and increase invasion and metastasis while inhibiting apoptotic cell death. K-RAS gene was found to be mutated codon in intestinal-type cancer, but not in diffuse-type cancer [21]. K-RAS gene mutations in H. Trastuzumab is a monoclonal antibody that binds to extracellular domain of the receptor, acting by blockage of the HER-2 receptor cleavage, inhibition of dimerization, and the induction of antibody-dependent cellular cytotoxicity ADCC. In phase III ToGA trial, the addition of trastuzumab to standard cisplatin and 5-fluorouracil improved overall survival from Similarly, in phase III REAL-3 trial, the addition of panitumumab fully humanized monoclonal anti-EGFR antibody to epirubicin, oxaliplatin, and capecitabine did not improve overall survival in patients with advanced gastric adenocarcinoma [25]. In addition, retrospective biomarker analysis has failed to identify a clear patient subset that would derive benefit from EGFR-directed therapies. In this study, median survival was reportedly 5. Tumor-Suppressor Genes The p53 tumor-suppressor gene, the guardian of human genome, is frequently inactivated in the tissue of gastric cancer as well as in preneoplastic lesions, by loss of heterozygosity LOH , missense mutation, or frame-shift deletions [12]. Activation of p53 also arrests the cell cycle to allow enough time for fixation of DNA damage. However, if DNA damage is beyond repair, p53 induces apoptotic cell death. The mutations of p53 have also been identified in gastric adenoma and intestinal metaplasia. We have recently reported that p53 downregulation due to increased MDM2-phosphorylation induces autophagy, which causes CagA oncoprotein degradation translocated from the bacterial body of H. APC is a multidomain protein with binding sites for numerous proteins including Wnt signaling pathway. APC plays major role in cell adhesion, cell migration, spindle formation, and chromosome segregation [28]. The mutations of APC have also been identified in gastric adenoma and intestinal metaplasia, indicating that they occur during preneoplastic stage of gastric cancer development. LOH and mutations of phosphatase and tensin homolog PTEN were observed in gastric cancers as well as in precancerous lesions [30]. DNA Methylation Methylation of CpG islands in a promoter region inhibits gene transcription by interfering with transcriptional initiation and serves as an alternative mechanism of inactivating tumor suppressor genes without gene mutation. Among factors known to cause aberrant DNA methylation, aging and chronic inflammation are known to promote the accumulation of DNA methylation. DNA methylation inactivates tumor suppressor genes without gene mutation. Chronic inflammation by H. Recent meta-analysis revealed that the frequencies of p16 promoter methylation in gastric cancer tissue were higher than those of normal and adjacent tissues [Normal: Furthermore, significant associations of p16 promoter methylation with TNM stage, histologic grade, invasive grade, and lymph node metastasis are shown TNM stage: Forkhead box Fox proteins comprise an evolutionarily conserved family of transcriptional regulators. Recent methylation profile analyses revealed that FOXD3-mediated transcriptional control of tumor suppressors is deregulated by H. Alternatively, CagA enhanced DNA methyltransferase 3B and enhancer of zeste homologue 2 expression, which resulted in the attenuation of let-7 expression by histone and DNA methylation [34]. Aberrant epigenetic silencing of let-7 expression leads to Ras upregulation. DNA methylation levels of specific CpG islands are associated with risk of gastric cancer. Angiogenesis Elevated concentrations of vascular endothelial growth factor VEGF have been described in patients with advanced gastric cancer and correlated with decreased survival. Median survival was 5. Apatinib, inhibitor of VEGF-2, showed improved progression free survival and overall survival in heavily pretreated patients with metastatic gastric cancer in phase II trial [40]. Phase III trial of apatinib is ongoing. Recent studies have shown that a considerable number of microRNAs are altered following infection with H. MicroRNAs that function as oncogenes, including miR, miR, and miRa, were upregulated, whereas microRNAs that function as tumor suppressors, such as miR, miR, miR, miR, and let-7a, were downregulated in gastric cancer [42 , 43]. MicroRNA deregulation is not completely reversible by eradication alone in long-term H. Runt domain

transcription factor 3 RUNX3 is a tumor suppressor, that is silenced in cancer via hypermethylation of its promoter. Previously, we reported that H. Recently, Wang et al. Cancer Stem Cell Cancer stem cells have been defined as a unique subpopulation in tumors that possess the ability to initiate tumor growth and sustain tumor self-renewal. Gastric cancer stem cells were first isolated and identified in These cells have the ability for self-regeneration and resistance for chemotherapy- or radiation-induced cell death. Cancer stem cells-targeted therapy is a novel direction for treating and preventing gastric cancer. In our recent study, translocated CagA from H. The high expression of CD44 is positively correlated with malignant transformation, metastasis, and relapse of gastric cancer [50]. We previously reported that the recurrence rate of early gastric cancer was significantly higher in the CD44v9-positive than the CD44v9-negative cohorts hazard ratio, CD44v9 expression in the tissue of primary gastric cancer represents a potential predictive marker for recurrence. Additionally, there is another hypothesis. It is thought that gastric cancer stem cells are derived from bone-marrow-derived mesenchymal stem cells. When there is injury, the bone-marrow-derived mesenchymal stem cells can mobilize from the bone marrow and participate in tissue repair. The results suggest that bone-marrow-derived mesenchymal stem cells are the source of gastric cancer. Conclusion As shown in this review, molecular mechanisms of gastric carcinogenesis have been extensively studied. Alterations in multiple genes and complex copy number and gene expression profiles have been identified in gastric cancer over the two decades. New strategies had been developed for advanced gastric cancer treatment. Conflict of Interests The authors declare that there is no conflict of interests regarding the publication of this paper. Acknowledgments We would like to thank Drs. Takanori Kanai and Naohisa Yahagi for their comments to the final version of the paper. Gastrointestinal and Liver Physiology, vol.

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2: Carcinogenesis - Wikipedia

Chemoprevention of Gastric Carcinogenesis The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government.

Higher diversity and higher composition of S. The stomach was considered as a sterile organ due to acid production. Accumulation and activation of these cells is induced by the local production of chemokines, cytokine, and NO generation. Recent advances in next-generation sequencing technology have revealed a complex gastric microbiome which may contribute to the development of gastric carcinogenesis. Our previous studies revealed that gastric microbiota were different according to HP infection status and presence or absence of gastric cancer in gastric mucosa by using a pyrosequencing method. There is a close interaction or battle between this acid secretion and HP. On the contrary to the usual concept, HP is neutralophiles. However, when atrophy and intestinal metaplasia occur, then HP itself decreases to colonize in the stomach 17 and eventually diversity of microbiota increases due to higher pH of gastric juice. From this background, we made a hypothesis that gastric microbiota could be different between in the antrum and in the body. Although we found a minor role of non-HP bacteria in the gastric carcinogenesis in the antrum, 12 the microbiota analysis from body could be different. Thus the aim of our study is to investigate the difference of human gastric microbiota between antrum and body according to disease control vs. Study subjects and gastric tissue specimen collection Gastric biopsies were collected from 12 subjects who underwent standard endoscopy to screen for premalignant or malignant gastric mucosal lesions or received endoscopy due to dyspepsia. Gastric mucosal antrum and body biopsies and blood samples were obtained from each patient during endoscopy from October to March at Seoul National University Bundang Hospital. Ten biopsy specimens per subjects were obtained to perform HP tests and pyrosequencing as our previous study. Histological features of gastric mucosa were recorded as the updated Sydney scoring system i. Written informed consent was obtained from all of the participants. Current HP infection was positive from any of the former three tests. In order to distinguish if the infection is an existing one, the following two methods were used: If all the 5 tests were negative, we would have regarded the subject as HP-negative. Besides, by using a Latex-enhanced Turbidimetric Immunoassay Shima Laboratories, Tokyo, Japan , serum concentrations of Pepsinogen I and II were evaluated, which are known to be associated with the severity of gastric atrophy. Bacterial genomic DNA extraction The antrum and body mucosal samples from 12 subjects were subjected to pyrosequencing. The sequencing was performed at Chunlab Inc. Pyrosequencing data analysis The primary analysis was conducted as described above. Reads taken from different samples were classified by unique barcodes of each PCR product. After identifying the target region in barcoded primers 9F or R , all of the linked sequences including adapter, barcode and linker were eliminated. Potential chimeric sequences were confirmed by the Bellerophon formula, which compares the BLASTN search conclusions between the forward half and reverse half sequences. Evaluation of species richness and diversity The species richness of samples was determined using the CLcommunity program Chunlab Inc. Random subsampling was conducted to equalize the read size of samples to compare the different read size within samples. Statistical analysis Comparisons between continuous parameters were performed by Kruskal-Wallis test and Mann-Whitney test. Baseline characteristics of clinical results of gastric antrum and body mucosa samples are shown in Table 1. However, there was no significant difference between the two groups.

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Excessive oxidative stress can damage DNA in gastric epithelial cells, indicating its possible involvement in gastric carcinogenesis. Gastric cancer arises from multiple genetic and epigenetic alterations in oncogenes, tumor-suppressor genes, cell cycle regulators, cell-adhesion molecules, and DNA repair genes.

Helicobacter pylori colonizes the majority of persons worldwide, and the ensuing gastric inflammatory response is the strongest singular risk factor for peptic ulceration and gastric cancer. However, only a fraction of colonized individuals ever develop clinically significant outcomes. Relevance in Helicobacter pylori associated gastric carcinogenesis. Gastric cancer ranks fifth in GLOBOCON cancer fact sheets among the most common cancers in prevalence, and is caused by Heliocobacter pylori its main etiological factor. Helicobacter pylori, a Gram-negative bacterial species selectively colonizes gastric epithelium. Bacterial, environmental and host genetic factors combine to define the degree of gastric damage. Helicobacter pylori colonizes the majority of persons worldwide, and the ensuing gastric inflammatory response is the strongest singular risk factor from peptic ulceration to gastric cancer. However, only a fraction of colonized individuals ever develop clinically significant outcomes like gastric cancer. In this cascade, host genetic and environmental factors interact to modulate the transition from one step to the next. The progression of gastric carcinoma and significance of H. Sustained interactions between H. Several recent studies proposed a distinct sequence for H. Several key issues that still need to be clarified, such as which virulence factors of H. According to El-Omar et al. The study of such host-bacterial interaction is key to uncover the molecular and cellular pathways involved and will ultimately lead to developing preventive and therapeutic strategies against this global killer. The differences in prevalence of gastric cancer have been explained as a multifactorial process with an interaction involving both infection with Helicobacter pylori as a triggering factor and host genetic susceptibility as an important explanation for inter individual variation in gastric cancer risk. Host factors in particular, genetic polymorphism in adaptive and innate immunity response gene sseem to increase the risk of gastric cancer largely through the induction of severe gastritis. Host genetic polymorphism study may help identify individuals at high risk of developing gastric cancer so that early intervention may be taken to help prevent its development. Recently, El Omar et al. A classic example of this paradigm is the study of a Caucasian population. Regarding the IL1RN gene, a variable number tandem repeat VNTR polymorphism has been detected within intron 2, and five allelic variants have been identified in the number of repeats varying from 2 to 6 El-Omar, The ability of H. Most of the single nucleotide polymorphisms SNPs studied are situated in the gene promoter region and play important roles in modulating gene expression. In short this H. Future prospective and Conclusion The polymorphisms in host genetic elements have brought us new prognostic and diagnostic prospective in gastric carcinogenesis research and study. Genetic profiling combined with H. Such a strategy is the only way to be ahead of this global killer and to abash it down.

4: Oral, Gastric Bugs May Help Pinpoint Stomach Cancer | Medpage Today

In most patients, gastric cancer is diagnosed in advanced stage. Curative treatment options are limited and the mortality is high. The process of gastric carcinogenesis is triggered by Helicobacter pylori-driven gastritis and is further characterized by its complexity of interaction with other risk.

There are two general types of gastric adenocarcinoma: The intestinal type is more common and is more often located in the distal part of the stomach. In contrast, the diffuse type has a poorer prognosis; generally occurs in younger patients; and can occur anywhere in the stomach, but especially in the cardia. The intestinal type is frequently accompanied by liver metastasis, whereas because the diffuse type has an increased propensity for intra- and trans-mural spread, it has been associated with peritoneal dissemination and poorer prognosis[1]. The diffuse type of gastric cancer shows more poorly differentiated cells than the intestinal type[11]. Intestinal-type adenocarcinoma is preceded by metaplastic changes, whereas diffuse-type adenocarcinoma is thought to arise in normal gastric mucosa. Gastric adenocarcinoma can also be divided into two groups, known as "differentiated" and "undifferentiated", using the Nakamura classification system[12]. Intestinal-type adenocarcinoma is considered to be essentially equivalent to differentiated adenocarcinoma, as is diffuse-type equivalent to the undifferentiated adenocarcinoma. However, some cases of intestinal-type adenocarcinoma also arise from the gastric mucosa without intestinal metaplasia IM. So based on the type of IM, some authors suggest that gastric cancer phenotypes can be classified into four groups depending on the marker combinations as: Gastric-type differentiated adenocarcinomas can be distinguished from other types of differentiated adenocarcinomas on the basis of their increased malignant potential in the incipient phase of invasion and metastasis[13]. The mucous epithelium of the stomach represents a major barrier to the various noxious agents by means of intercellular tight junctions. This epithelium and its components are also vital for complex communications and physiological functions[14]. Histologically, the human gastric mucosa is divided into three regions: The epithelium of these regions is composed of millions of glands that are surrounded by supporting stromal cells which are derived from mesenchyme. In the corpus, glands are long and composed of several epithelial cell types, including surface mucous foveolar cells pit cells , acid-making oxyntic parietal cells, mucous neck cells intermediate progenitor for chief cells , zymogenic chief cells, and hormone-secreting endocrine cells. In the antrum, the shorter glands are composed mainly of mucus-secreting cells and endocrine cells that secrete hormones such as gastrin and somatostatin. The stomach mesenchymal compartment surrounding the glands is less studied and little understood[15 - 18]. The human stomach mucosal tubular glands are further subdivided into foveolus, isthmus, neck and base regions. The gastric glands open into the bottom of the pits, on an average with 4 to 5 glands per pit. Fundic glands are quite straight, whereas antral glands are branched and coiled in their basal ends. Fundic and antral units combination of a pit and a gland differ very much in their cell characteristics and turnover rates the human antral mucosa is known to have a much higher turnover rate. The antral unit contains surface mucous foveolar cells, antral gland cells, endocrine cells mainly gastrin-producing G-cells, but also EC and somatostatin-producing D cells , and occasional oxyntic cells. In the pylorus, the gastric glands contain many more mucinous cells, no zymogenic cells and few oxyntic cells Figure 1 [19 - 23]. In addition, it should be noted that the subepithelial mesenchymal cells and their secreted basement membrane factors compose the lamina propria. This constitutes a structural support while regulating epithelial cell function and epithelial cell networks[24 , 25]. The gastrointestinal tract has rapid epithelial turnover and exposure to injury by infections and dietary toxins. These conditions create very high cancer prevalence. Neoplasia can follow cellular metaplasia due to chronic inflammation, injury and repair[32]. This is the most documented process for gastric cancer[33 - 35]. An acceptable concept is that there are two corner-stones with regard to this process. Marshall and Warren in [37]. Beginning with some of the earliest observations in cancer biology, it appears that chronic inflammation stimulates tumor development and plays a critical role in initiating, sustaining and advancing tumor growth[39 , 40]. Direct effect of the viral pathogens on neoplastic transformation of epithelial cells has been shown; however, it is also evident that not all inflammation is tumorigenic[41]. In the acute phase of inflammation,

the release of endogenous reactive oxygen and nitrogen species O2-, H2O2, NO, OH, ONOO-, HOCl from such innate immune cells as macrophages and leukocytes plays an important role in the elimination of pathogens[42]. However, when present chronically, this can induce DNA damage in proliferating cells. In addition, it is also possible for other bacteria to colonize the stomach and additionally trigger carcinogenesis by gastric atrophy result of chronic inflammation which represents a loss of gastric glands and associated lower acidity of gastric juice[43 , 44]. Hypoacidity associated with H. Another important point that should be added is that H. The inverse association of H. Furthermore, mast cells in particular play an important role in attracting inflammatory cells by releasing inflammatory mediators. Monocytes differentiate into macrophages, and become activated in response to local chemokine and cytokine interactions[51]. Also, the correlation between tumor-associated macrophage abundance and poor prognosis has been shown[52]. Furthermore, macrophage-deficient mice display reduced progression of tumors to a more malignant phenotype[53]. Recently, direct evidence has also linked IL-6 to inflammation-mediated tumor initiation and proliferation in colon cancer[54]. Cytokines also affect cell death and cell cycle pathways[55 , 56]. It is also produced by tumor cells. However, if it is produced chronically, it can act as a tumor promoter by contributing to tissue remodeling and stromal development[57 , 58]. The activation of these pathways results in further cytokine release[57 , 59 , 60]. Activation of the innate immune system is followed by the adaptive immune response. The presence of a Th1, rather than a Th2, immune response is also associated with better survival in gastric cancer patients[36]. Although the subsequent pathways are different, chronic inflammation is the first step in both the intestinal and the diffuse type of gastric cancer. While the intestinal type has a sequence of multifocal atrophic gastritis, IM and dysplasia, which advances to carcinoma, the diffuse type tends to be primarily genetic in origin[61 , 62]. The progress from IM to gastric cancer has a wide range of molecular alterations affecting transcription factors, such as CDX1 and CDX2, telomerases, microsatellite instability, mutations of p53 protein, overexpression of COX-2, cyclin D2, and decreased expression of p27[63]. The next step is gastric dysplasia. During the progression of normal tissue through the metaplasia-dysplasia sequence, there are mutations in genes including p53, also loss of heterozygosity of the adenomatous polyposis coli gene, overexpression of the antiapoptotic gene bcl-2 and a mixture of polyploidy and aneuploidy[63]. Inflammation also plays an important role in the ability of tumor cells to invade and metastasize. The ability of epithelial tumor cells which metastasize to express specific chemokine receptors has been shown[64]. Paracrine secretion of pro-inflammatory cytokines i. During the later stages, additional mutations can be acquired, and this leads to the cancer cell gaining a further growth advantage and acquiring a more malignant phenotype[66 , 67]. COX2 is upregulated in the gastric epithelium and in the infiltrating inflammatory cells in the stomach during gastritis[68 - 70]. Furthermore, it has been shown that sulindac, a nonsteroidal anti-inflammatory drug, suppresses the progression of gastric cancer in mice[71]. Hence, a K-ras activation-induced inflammatory response may facilitate the formation of IM and promote the progression of gastric cancer. It can be defined as a corpus lesion. Increase in mucus and loss of mature parietal and chief cells in humans correlates with SPEM Figure 2 [73]. SPEM is characterized by expression of TFF2 spasmolytic polypeptide which is normally a product of mucous neck cells and antral gland cells[72]. SPEM also arises from a second proliferative zone at the bases of metaplastic fundic units, either by transdifferentiation of chief cells or activation of an unknown basal crypt progenitor[76 , 77]. However, it is not clear whether these cells are related to the gastric progenitor cells[78]. Spasmolytic polypeptide-expressing metaplasia; TFF Trefoil family factor 2. It must be noted that an important factor for the development of gastrointestinal cancers is peritumoral stroma. Activated fibroblasts within the stroma can help to create an environment containing vessels and infiltrating inflammatory cells and it is the interaction between these different cell types which is permissive of tumor growth, angiogenesis, and invasion[79 - 81]. The question that must be answered is: The interpretation that the metaplasia is an intermediate step in the development of gastric cancer may be facile, because different types of IM have different degrees of association with malignancy, and early stage gastric cancers can arise in nonintestinalized epithelium[82 - 84]. Investigators have reported that solid cancers might originate from differentiated cells and they have reported the possible existence of cancer stem cells CSCs or tumor initiating cells in solid malignant tumors[

85 , 86]. However, based on the assessment of the differentiation status of tumor cells, they appear to deviate little from their normal progenitors and to show similar differentiation programs. Studies on tissues undergoing continuous cell renewal suggest that cancer cells may originate from a stem cell compartment[87]. The origin of human gastric CSCs has yet to be elucidated, but data obtained from a mouse model of Helicobacter-induced gastric cancer have implicated bone marrow-derived cells as a potential candidate. Further studies focusing on the identification and characterization of CSCs in gastric cancer may lead to novel diagnostic and therapeutic tools, dramatically improving the prognosis of gastric cancer patients. Cancer burden in the year Benefit of adjuvant chemotherapy for resectable gastric cancer: Dietary intake of selected micronutrients and gastric cancer risk: High salt diets dose-dependently promote gastric chemical carcinogenesis in Helicobacter pylori-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. Salt and gastric adenocarcinoma: Cancer Epidemiol Biomarkers Prev. World Health Organization classification of tumours. Pathology and genetics of tumours of the digestive system. The two histological main types of gastric carcinoma: Acta Pathol Microbiol Scand. Cellular and molecular aspects of gastric cancer. Gastric mucosal defense and cytoprotection: Carcinoma of the stomach in incipient phase: Mucin phenotype of gastric cancer and clinicopathology of gastric-type differentiated adenocarcinoma. Current molecular markers for gastric progenitor cells and gastric cancer stem cells. Cells intermediate between mucous neck cells and chief cells in rat stomach. Gastric endocrine cells share a clonal origin with other gut cell lineages. The mucous neck cell in the human gastric corpus: Epithelial stem cell repertoire in the gut: Int J Exp Pathol.

5: Carcinogen - Wikipedia

Cancer is a major public health problem and at the beginning of the 19th century, gastric cancer was the second most common cancer worldwide[].Every year there are new cases and gastric cancer-related deaths in the world[].

Mutation rates strongly increase in cells defective in DNA mismatch repair [20] [21] or in homologous recombinational repair HRR. In addition, faulty repair of these accumulated DNA damages may give rise to epimutations. Non-mainstream theories[edit] There are a number of theories of carcinogenesis and cancer treatment that fall outside the mainstream of scientific opinion, due to lack of scientific rationale, logic, or evidence base. These theories may be used to justify various alternative cancer treatments. They should be distinguished from those theories of carcinogenesis that have a logical basis within mainstream cancer biology, and from which conventionally testable hypotheses can be made. Several alternative theories of carcinogenesis, however, are based on scientific evidence and are increasingly being acknowledged. Some researchers believe that cancer may be caused by aneuploidy numerical and structural abnormalities in chromosomes [52] rather than by mutations or epimutations. Cancer has also been considered as a metabolic disease in which the cellular metabolism of oxygen is diverted from the pathway that generates energy oxidative phosphorylation to the pathway that generates reactive oxygen species figure. Aberrant DNA methylation patterns â€" hypermethylation and hypomethylation compared to normal tissue â€" have been associated with a large number of human malignancies. See DNA methylation in cancer A number of authors have questioned the assumption that cancers result from sequential random mutations as oversimplistic, suggesting instead that cancer results from a failure of the body to inhibit an innate, programmed proliferative tendency. These genes still exist within the genome of more complex metazoans , such as humans, although more recently evolved genes keep them in check. When the newer controlling genes fail for whatever reason, the cell can revert to its more primitive programming and reproduce out of control. The theory is an alternative to the notion that cancers begin with rogue cells that undergo evolution within the body. Instead they possess a fixed number of primitive genes that are progressively activated, giving them finite variability. Cancer now originates when a rare somatic mutation recombines such fragments into a functional driver of cell proliferation. Often, the multiple genetic changes that result in cancer may take many years to accumulate. During this time, the biological behavior of the pre-malignant cells slowly change from the properties of normal cells to cancer-like properties. Pre-malignant tissue can have a distinctive appearance under the microscope. Among the distinguishing traits are an increased number of dividing cells, variation in nuclear size and shape, variation in cell size and shape, loss of specialized cell features, and loss of normal tissue organization. Dysplasia is an abnormal type of excessive cell proliferation characterized by loss of normal tissue arrangement and cell structure in pre-malignant cells. These early neoplastic changes must be distinguished from hyperplasia , a reversible increase in cell division caused by an external stimulus, such as a hormonal imbalance or chronic irritation. The most severe cases of dysplasia are referred to as " carcinoma in situ. Nevertheless, carcinoma in situ may develop into an invasive malignancy and is usually removed surgically, if possible. Somatic evolution in cancer Just like a population of animals undergoes evolution , an unchecked population of cells also can undergo evolution. This undesirable process is called somatic evolution , and is how cancer arises and becomes more malignant. However once cancer begins, cancer cells undergo a process of natural selection: This evolution is why cancer recurrences will have cells that have acquired cancer-drug resistance or in some cases, resistance to radiation from radiotherapy. Biological properties of cancer cells[edit] In a article by Hanahan and Weinberg , the biological properties of malignant tumor cells were summarized as follows: Loss of sensitivity to anti-growth signals, also leading to unchecked growth. Loss of capacity for apoptosis , in order to allow growth despite genetic errors and external anti-growth signals. Loss of capacity for senescence , leading to limitless replicative potential immortality Acquisition of sustained angiogenesis , allowing the tumor to grow beyond the limitations of passive nutrient diffusion. Acquisition of ability to invade neighbouring tissues , the defining property of invasive carcinoma. Acquisition of ability to build metastases at distant sites, the classical property of malignant tumors

carcinomas or others. The completion of these multiple steps would be a very rare event without: Loss of capacity to repair genetic errors, leading to an increased mutation rate genomic instability , thus accelerating all the other changes. These biological changes are classical in carcinomas ; other malignant tumors may not need to achieve them all. For example, tissue invasion and displacement to distant sites are normal properties of leukocytes ; these steps are not needed in the development of leukemia. The different steps do not necessarily represent individual mutations. For example, inactivation of a single gene, coding for the p53 protein, will cause genomic instability, evasion of apoptosis and increased angiogenesis. Not all the cancer cells are dividing. Rather, a subset of the cells in a tumor, called cancer stem cells , replicate themselves and generate differentiated cells. Failure of this mutual regulation between genetic reprogramming and cell interactions allows cancer cells to give rise to metastasis. Cancer cells respond aberrantly to cytokines, and activate signal cascades that can protect them from the immune system. Typically, a series of several mutations to these genes is required before a normal cell transforms into a cancer cell. This concept is sometimes termed "oncoevolution. But the uncontrolled cell division that characterizes cancer also requires that the dividing cell duplicates all its cellular components to create two daughter cells. The activation of anaerobic glycolysis the Warburg effect , which is not necessarily induced by mutations in proto-oncogenes and tumor suppressor genes, [86] provides most of the building blocks required to duplicate the cellular components of a dividing cell and, therefore, is also essential for carcinogenesis. Many can produce hormones , a "chemical messenger" between cells that encourage mitosis , the effect of which depends on the signal transduction of the receiving tissue or cells. In other words, when a hormone receptor on a recipient cell is stimulated, the signal is conducted from the surface of the cell to the cell nucleus to affect some change in gene transcription regulation at the nuclear level. Some oncogenes are part of the signal transduction system itself, or the signal receptors in cells and tissues themselves, thus controlling the sensitivity to such hormones. Oncogenes often produce mitogens , or are involved in transcription of DNA in protein synthesis , which creates the proteins and enzymes responsible for producing the products and biochemicals cells use and interact with. Mutations in proto-oncogenes, which are the normally quiescent counterparts of oncogenes , can modify their expression and function, increasing the amount or activity of the product protein. When this happens, the proto-oncogenes become oncogenes , and this transition upsets the normal balance of cell cycle regulation in the cell, making uncontrolled growth possible. The chance of cancer cannot be reduced by removing proto-oncogenes from the genome , even if this were possible, as they are critical for growth, repair and homeostasis of the organism. It is only when they become mutated that the signals for growth become excessive. One of the first oncogenes to be defined in cancer research is the ras oncogene. Many can produce hormones , "chemical messengers" between cells that encourage mitosis, the effect of which depends on the signal transduction of the receiving tissue or cells. Some are responsible for the signal transduction system and signal receptors in cells and tissues themselves, thus controlling the sensitivity to such hormones. They often produce mitogens , or are involved in transcription of DNA in protein synthesis , which create the proteins and enzymes is responsible for producing the products and biochemicals cells use and interact with. Mutations in proto-oncogenes can modify their expression and function, increasing the amount or activity of the product protein. When this happens, they become oncogenes , and, thus, cells have a higher chance to divide excessively and uncontrollably. The chance of cancer cannot be reduced by removing proto-oncogenes from the genome , as they are critical for growth, repair and homeostasis of the body. It is important to note that a gene possessing a growth-promoting role may increase carcinogenic potential of a cell, under the condition that all necessary cellular mechanisms that permit growth are activated. If the condition is not fulfilled, the cell may cease to grow and can proceed to die. This makes knowledge of the stage and type of cancer cell that grows under the control of a given oncogene crucial for the development of treatment strategies. Tumor suppressor genes[edit] Many tumor suppressor genes effect signal transduction pathways that regulate apoptosis , also known as "programmed cell death". Tumor suppressor genes code for anti-proliferation signals and proteins that suppress mitosis and cell growth. Generally, tumor suppressors are transcription factors that are activated by cellular stress or DNA damage. Often DNA damage will cause the presence of free-floating genetic material as well as other signs, and will trigger enzymes and pathways that lead to the

activation of tumor suppressor genes. The functions of such genes is to arrest the progression of the cell cycle in order to carry out DNA repair, preventing mutations from being passed on to daughter cells. The p53 protein, one of the most important studied tumor suppressor genes, is a transcription factor activated by many cellular stressors including hypoxia and ultraviolet radiation damage. Despite nearly half of all cancers possibly involving alterations in p53, its tumor suppressor function is poorly understood. The Warburg hypothesis is the preferential use of glycolysis for energy to sustain cancer growth. The invariable consequence of this is that DNA repair is hindered or inhibited: DNA damage accumulates without repair, inevitably leading to cancer. Mutations of tumor suppressor genes that occur in germline cells are passed along to offspring , and increase the likelihood for cancer diagnoses in subsequent generations. Members of these families have increased incidence and decreased latency of multiple tumors. The tumor types are typical for each type of tumor suppressor gene mutation, with some mutations causing particular cancers, and other mutations causing others. The mode of inheritance of mutant tumor suppressors is that an affected member inherits a defective copy from one parent, and a normal copy from the other. For instance, individuals who inherit one mutant p53 allele and are therefore heterozygous for mutated p53 can develop melanomas and pancreatic cancer , known as Li-Fraumeni syndrome. Other inherited tumor suppressor gene syndromes include Rb mutations, linked to retinoblastoma , and APC gene mutations, linked to adenopolyposis colon cancer. Adenopolyposis colon cancer is associated with thousands of polyps in colon while young, leading to colon cancer at a relatively early age. Development of cancer was proposed in to depend on at least two mutational events. Each cell has two copies of the same gene, one from each parent, and under most cases gain of function mutations in just one copy of a particular proto-oncogene is enough to make that gene a true oncogene. On the other hand, loss of function mutations need to happen in both copies of a tumor suppressor gene to render that gene completely non-functional. However, cases exist in which one mutated copy of a tumor suppressor gene can render the other, wild-type copy non-functional. This phenomenon is called the dominant negative effect and is observed in many p53 mutations. Inactivation of one allele of some tumor suppressor genes is sufficient to cause tumors. This phenomenon is called haploinsufficiency and has been demonstrated by a number of experimental approaches. Tumors caused by haploinsufficiency usually have a later age of onset when compared with those by a two hit process. For example, a mutation limited to one oncogene would be suppressed by normal mitosis control and tumor suppressor genes, first hypothesised by the Knudson hypothesis. It is only when enough proto-oncogenes have mutated into oncogenes, and enough tumor suppressor genes deactivated or damaged, that the signals for cell growth overwhelm the signals to regulate it, that cell growth quickly spirals out of control. Often, because these genes regulate the processes that prevent most damage to genes themselves, the rate of mutations increases as one gets older, because DNA damage forms a feedback loop. Mutation of tumor suppressor genes that are passed on to the next generation of not merely cells, but their offspring , can cause increased likelihoods for cancers to be inherited. Members within these families have increased incidence and decreased latency of multiple tumors. The mode of inheritance of mutant tumor suppressors is that affected member inherits a defective copy from one parent, and a normal copy from another. Because mutations in tumor suppressors act in a recessive manner note, however, there are exceptions , the loss of the normal copy creates the cancer phenotype. For instance, individuals that are heterozygous for p53 mutations are often victims of Li-Fraumeni syndrome , and that are heterozygous for Rb mutations develop retinoblastoma. In similar fashion, mutations in the adenomatous polyposis coli gene are linked to adenopolyposis colon cancer , with thousands of polyps in the colon while young, whereas mutations in BRCA1 and BRCA2 lead to early onset of breast cancer.

6: Molecular Pathobiology of Gastric Carcinogenesis - Wael El-Rifai

Gastric cancer is the third leading cause of cancer-associated death worldwide. The global cancer statistics report indicated an estimated , new gastric cancer cases and , deaths occurred in

7: Host Genetic Factors: Relevance in Helicobacter Pylori Associated Gastric Carcinogenesis

gastric carcinogenesis through upregulation of DNA damage [50]. Inhibition of H. pylori -induced gastritis and oxidative stress is considered as one of the promising approaches to prevent gastric cancer.

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