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Gastric cancer stem cell: Carcinogenesis and targeted personalized therapies of cancer stem cell

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Abstract. Gastric cancer (GC) is one of the most common cancers in worldwide range which ranks fifth, and it is also third most common cancerous death reason. Although there has been a decline in the rate of incidence and mortality over recent fifty years, cure for GC is extremely hard to achieve. The symptoms are not conspicuous at early stage of the GC patients usually, which is the reason GC is diagnosed at terminal stage. And it is worse that the prognosis effect is outrageously bad, the median survival times are mostly less than a year. Under this condition, prevention is the most efficient method to reduce the incidence and mortality, meanwhile, the application of newly emerged therapy should be attached importance to GC. To create accurate treatment to achieve this goal, it is necessary to comprehend the mechanism of the carcinogenesis, and mechanism of cancer development, the critical transformation points derived from those mechanism will divide the different methodology applying period. This article mainly focuses on the cancer stem cell (CSC) aspect of carcinogenesis, cancer development to inform the points which can be utilized to intervene and new therapy method.

Keyword: gastric cancer, carcinogenesis, cancer stem cell (CSC), targeted personalized therapy.

1. Introduction

1.1. Introduction of cancer stem cell model

The cancer stem cell model declares that only some subgroups of cancerous cells dominate the formation, self-reproduction, and differentiation of tumor, while the daughter cells only has restricted proliferate ability because epigenetic regulation occurred [1]. It is analogous to the structure of normal human tissue including the stem cell responsible for differentiation and other heterogeneous cells, however, those cells are not in order like normal organ [2]. This model forecast an inspiring future for eliminate the tumor without killing all the cancerous cells like radiotherapy and chemotherapy by removing the cancer stem cells (CSCs) specifically. Unlike traditional therapy will kill normal cells simultaneously if the targeted cells can be identified precisely, CSC targeted cell therapy can reduce the developing potential with much less harm. However, the features to determine the CSC are key difficulty in target therapy. The biomarks found in gastric CSC do not have enough specifications to distinguish them from normal stem cells [3]. Other methods like side population methods are also highly valid. The reasons why it is intricate to specialize the CSC are mainly caused by the plasticity of CSC. The silence of CSC properties

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is reversible during the process of the traditional therapy like radiation [4]. Hence, it is necessary to be cautious to combine radiation therapy and targeted therapy.

1.2. Introduction of the gastric carcinogenesis

In GC, there are long-term and multiple-step processes called correa's cascade including metaplasia and dysplasia caused by atrophic gastritis, then, gastric cancer [5], meanwhile, surgery is still primary treatment of cancer stage and complete cut is the sole operation to achieve totally recover [6], the manifestation of the patients after treatment is not satisfying, high mortality mainly aroused by metastasis, Chemotherapy resistance [7, 8]. In this condition, precautionary measurements are vital to decrease the morbidity of GC in the present stage to stop the progression of the tumor formation. To attain this objective, the process of the whole gastric carcinogenesis should be evaluated.

1.3. Metaplasia

It is a common lesion during the formation of tumor, and highly related to the intestinal type GC, another type is diffuse type which is more determined by inheritance [9,10]. *Helicobacter pylori* genomics are considered as the main factor to trigger correa's cascade, host genetic factors ABO blood type, genetic predisposition, environmental influence, diet, and intestinal microbiota are other causes [11].

As consequence of the infection of *Helicobacter pylori*, gastritis happens, and if it is atrophic it will cause the loss of glandular oxyntic mucosa due to long-range inflammation [12]. Finally, the gastric epithelial cells act like intestinal phenotype cells, containing eosinophilic enterocytes with a distinct brush border (apical microvilli to promote digestion) and goblet cells formed sufficiently [13]. Some research had indicated that the intestinal metaplasia spread is related to the gastric crypts [14].

In this carcinogenesis stage, the personalized targeted treatments are under exploration for diagnosis, treatment, and the goal of prognosis. To establish the method of personalized treatments and measurement of potential of evolution to invasive carcinoma, the biomarkers and the molecule pathway should be illustrated. Novel diagnostic could expound polymorphisms in genes, alteration in the expression of miRNAs and lncRNAs, as well as microbiome happened in this stage [15], meanwhile, the corresponding transcription factor (CDX-1 protein), telomere reduction, microsatellite instability, and mutations in p53, APC, and K-Ras have been identified in Intestinal Metaplasia [16]. More clinic-related research and specific molecule pathways on those biomarkers could pave the way to stop carcinogenesis here.

1.4. Dysplasia

The dysplasia of gastric epithelial cells are considered as the portent of carcinoma, histologically evident neoplastic epithelium without tissue invasion, which are developed under the effect of atrophic gastritis and metaplasia [11,17]. In clinic research, the classification is quite complicated like Padova methodology placing emphasis on clinical application. Basically, the morphology of the dysplasia cells are characterized by neoplastic epithelium phenotype cells which are restricted to glandular structures inside the basilar membrane. Compared to metaplasia phase, the metaplastic glandular structures are not orderly—irregular shape equipped with thick membrane, mucus secretion shrinkage even shutoff, moreover, the nuclei of those cells are pseudo layered with evident amphophilic nucleoli [18].

Currently, there is evidence to indicate that the malignant tumor potential of the high- grade gastric dysplasia can reach 10% to100% [19]. Surgery (endoscopic mucosal resection), nowadays, this physical operation is the only way to restrain the carcinogenic progression on high- grade gastric dysplasia, meanwhile, endoscopic ultrasound and adequate sampling provided can ensure submucosal invasion is excluded [19]. Presently, the comprehensive system active mechanism of how the dysplastic epithelium evolve to invasive carcinoma, how the mutated cells expand to surrounding environment doesn't construct, consequently, the treatment scheme after endoscopic mucosal resection is still under exploration, that remains a hard problem to solve, always a risk of occurrence of synchronous or metachronous gastric neoplasms in other sites [20].

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The available scientific literature suggests that the eradication of H. pylori infection results in a modest deceleration of carcinogenesis. However, it is important to note that all available clinical trials have been conducted in adult subjects who were in advanced stages of atrophy and intestinal metaplasia, likely infected for a period of five or more decades. Nonetheless, recent research has postulated that the inflammatory process caused by H. pylori may lead to oxidative damage, which could contribute to neoplastic progression. It is plausible that oxidative insult may have been present in the gastric mucosa for a considerable period before the initiation of anti-Helicobacter treatment. Consequently, molecular events that eventually lead to neoplasia may have reached a point of irreversible transformation. [21].

Recently, the pathway of the gastric CSC formation from dysplastic epithelium has been discovered gradually, a step towards a comprehensive system active evolution pathway. This had stepped forward in discovering the origin of the gastric cancer stem cells, researchers found that the dysplastic stem cell (DSC) populations CD44v6neg/CD133/CD166 (DP) could be one target of CSCs ancestor. The dysplastic cell lineages are maintained and differentiate through a Wnt ligand-independent signaling pathway, mediated by CK1α/β-catenin. Xenograft studies demonstrated that the DP-DSCs clonally evolve towards multiple types of gastric adenocarcinomas and promote cancer cell heterogeneity by acquiring additional genetic mutations and recruiting the tumor microenvironment [22].

1.5. Invasive Carcinoma

Gastric cancer comes to mature tumor stage when invasive carcinoma is formed. The Lauren classification is widely accepted in this phase, what divided the invasive carcinoma into intestinal and diffuse types on account of the glandular structure [23]. In correa's cascade, the progressively increasing genetic and epigenetic alterations accumulated [24]. While clinical traits and gene alterations of the intestinal and diffuse GC types are different [23].

In intestinal tumors, tumor cells usually stick together, formed in tubular or glandular shape. It is common that this type is related to lymphatic or vascular invasion. Notably intestinal cancer has a better prognosis [25].

In diffuse gastric cancer, there exists more complicated problem to deal with, the tumor cells act more solitude behavior by lacking adhesion, representing as single cells or smaller group compared to intestinal type, and act as single cells or small subgroups dispersed among stomach. Peritoneal metastasis can be discovered in diffuse gastric cancer, otherwise, precursor lesions are hard to detect in diffuse type cancer [26].

It is immensely significant to illustrate molecule pathway of carcinogenesis, mutated gene expression products, those knowledge contributes to direction of personalized therapies to restrain the process of carcinogenesis, targeted pharmaceutical to eliminate CSCs, and clarification of clinical metastatic potential, prognosis, resistance to chemotherapeutic agents. One the other word, the abnormal genes and genetic information expression pathway could be the targeted for personalized therapy if the products are related to carcinogenesis.

By application of modern technique like microarrays and comparative genomic hybridization, the genetic anomaly incidents of chromosomes can be detected in gastric cancer, and the Wnt, TGF or E-cadherin signals had been approved the vital roles in carcinogenesis [27].

Genes deregulations are elaborated progressively as well. In intestinal gastric cancer, Microsatellite instability (MSI), mutation of KRAS and APC, and ERBB2 exaggeration, MLH1, MGMT, and CDKN2A genes silenced caused by CpG island hypermethylation are frequently found in intestinal type GC [23]. However, loss of heterozygosity at chromosome 17p (p53) and mutation or loss of E-cadherin are more often detected in the development of diffuse-type gastric cancer, and, metastasis of gastric tumor cells usually be regarded as the blame of loss of p27 and gene amplification of K-sam and c-met genes [28]. Those mutated genes are the origin of the differentiation of CSCs, and proliferation, adhesion, and migration of tumor cells, the ideal targeted point may hide in them.

2. Discussion

On account of the high relevance between H pylori infection and gastric carcinogenesis, scientists want to figure out the effect of reducing the H pylori infection, however, this operation just shows limited impediment of carcinogenesis, the possible trigger is the long-term oxidative damages induced by the inflammatory process have already generated sufficient molecule incidents to initiate correa's cascade [29].

Presently, primary therapeutic treatments in invasive tumors are still cases surgery, chemotherapies and radiotherapies, nevertheless, worldwide the 5-year survival rate remains at 25%, which is a unsatisfactory figure [30]. And only a marginal survival benefit caused by chemotherapy analyzed by meta-analyses of random trials [31]. It is relieved that, this situation can be illustrated by cancer stem cell theory, while the targeted therapy on cancerous stem cells may have brightness on successful cure. The principle of those chemotherapies and radiotherapies is inflicting DNA damage, then to trigger senescence in cancer cells, a method called therapy-induced senescence (TIS) resulting in lessening tumor size and accumulated immune cells such as neutrophils, monocytes as well as T-cells [32-34]. But the incompleteness of elimination of tumor cells remain potential trouble, those tumor cells what escape from TIS gains extra mutation to get stemness and evade senescence over a long-term course of TIS to rejuvenate tumor, besides, chemicals secretion of senescent cells always represent tumor-promoting factors [35,36].

Furthermore, the reasons why chemotherapy does not act as an excellent tool to cure gastric cancer are consistent with the modified model of the CSC theory, dynamic model, differentiated cell populations have the potential to reverse to CSC governed by tumor cell environment, specifically, governed by inducing factors produced by stromal cells [37].

Focus on the environment CSCs located, which are surrounded by a sheet of subepithelial myofibroblasts (SMFs), this niche is the source of growth and differentiation factors, in recent research, the fact that CSC could activate stromal fibroblasts (SFs) and become myofibroblasts had been shown, those transformed cells could emit vascular endothelial growth factor A (VEGFA) and other angiogenic factors, a promising preventing strategy inspired by this mechanism by restraining tumor cell-derived factors [38]. Understanding the origin of CSCs and their interaction with niches would be helpful for precisely targeting CSCs.

3. Conclusion

Those findings of molecule pathways of carcinogenesis, altered genetic information, and abnormal gene expression products construct the foundations for personalized treatment strategies. The targets of chemical pharmaceuticals and immunotherapy like the Car T cells method to stop carcinogenesis, reduce CSCs, and restrict metastasis are revealed while discovering the molecule pathway of carcinogenesis.

With the development of unambiguous mechanisms, findings of biomarkers, and the microenvironment of CSC, more options for scientists emerge to design experiments.

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