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Invited critical review

HSP72 and gp96 in gastroenterological cancers

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ABSTRACT

Heat shock protein 72 (HSP72) and glycoprotein 96 (gp96) are highly expressed in cancer tissues. Recent studies indicate the possible roles of HSP72 and gp96 in the development and progression of gastrointestinal carcinomas but detailed mechanisms are still ambiguous. Human esophageal cancer, gastric cancer, colon cancer and liver cancer are common gastrointestinal malignant carcinomas in the world. The studies indicated that there existed a significant correlation between the expression of HSP72, gp96 and the development and progression of digestive carcinomas. HSP72 and gp96 expression were significantly associated with the presence of tumor infiltration, lymph node and remote metastasis. Interestingly, studies have found that HSP72 chaperoned alpha-fetoprotein (AFP), HBx in hepatocellular carcinoma, and CD44 in colonic carcinomas. The further researches demonstrated that HSP72-AFP or gp96-AFP recombined vaccine could elicit specific anti-tumor immunity. The high-level expression of HSP72 and gp96 may be not only used as diagnostic or prognostic markers for gastrointestinal carcinomas but also as better immunotherapeutic vaccines in the cancers.

Contents

1. Introduction

The heat shock protein (HSP) family is a highly conserved group of cellular proteins and is up-regulated under stress conditions, such as heat, hypoxia, serum deprivation, neoplasia and virus infection [1–3]. It functions as molecular chaperone and biochemical regulator to mediate cell growth, apoptosis, protein homeostasis and cellular targets of peptides [2]. Aside from their response to heat shock and chemical or physical stress stimuli, HSPs have been reported to be over-expressed in a wide range of human tumors including breast, endometrial, ovarian, colon, lung and prostate cancers [4]. Studies have also shown that HSP expression have a close relationship with carcinoma progression [4,5]. They may combine with oncogene products to form complexes and transport them into intracellular special sites and promote cancer cell proliferation and heterogeneous differentiation [6,7]. Recent studies have also shown that HSP72 and gp96 are highly expressed in cancer tissues and have been used as prognostic markers in some tumors [8–14].

The study indicates the possible roles of HSP72 and gp96 in the development and progression of gastrointestinal carcinomas but detailed mechanisms are still ambiguous [15]. Gastroenterological cancers – esophageal squamous cell carcinoma, gastric adenocarcinoma, colonic adenocarcinoma and hepatocellular carcinoma – are four common malignant cancers. There may be a correlation between the progression of the carcinomas and over-expression of HSP72 and gp96, but now there are few reports about expression of HSP72 and gp96 in a series of

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gastrointestinal carcinomas. Recent researches investigated the immunohistochemical expression of HSP72 and gp96 proteins in tumoral specimens obtained from gastroenterological cancer patients and evaluated the association between the expression of HSP and various clinicopathological parameters, tumor proliferative capacity in these cancers. The results suggested that there existed a significant correlation between the expression of HSP72, gp96 and the progression in gastroenterological carcinomas.

2. Correlation between clinicopathology and expression of HSP72 and gp96 in gastroenterological carcinomas

Researches have shown that almost all of the detected primary gastrointestinal carcinomas highly expressed HSP72, and majority of tumors expressed gp96, which had significant differences compared with those in mucous membrane adjacent to cancers. There was a definite correlation between the expression of HSP72, gp96 and development of gastroenterological carcinomas.

The heat shock protein (HSP) family is a kind of highly conserved protein synthesized after heat induction or other stressors [1–3]. In mammalian cells, this system is divided into two predominant categories, which appear to be structurally and functionally related: the heat shock protein (HSP) and the glucose-regulated protein (grp) or glycoprotein (gp) [1]. During the growth and development of normal cells, HSP70 is constitutively expressed at low levels but the expression is dramatically enhanced by stressful conditions [2]. Heat shock protein 72, belonging to the family of HSP70, is a highly conserved protein synthesized under various stresses. In non-transformed cells at normal conditions, HSP72 is expressed at very low levels. It is, however, present at elevated levels in the major fraction of tumors and in many transformed cell lines [16–18]. It is commonly assumed that the expression of HSP72 at elevated levels in tumor cells is the consequence of oncogenic transformation and enhanced expression of HSP72 has a close relationship with epithelial carcinoma cells growth [16–18]. Up-regulated expression of the HSP70 family in tumor cells may be a requirement to serve as molecular chaperone in regulating and stabilizing oncofetal protein and mutant oncogene products during tumor growth process [19–21]. In normal cells, gp96 expression could also be induced by various stresses to function as molecular chaperone [20,21]. Some researches have implied that enhanced expression of gp96 has a close relationship with cancer cells growth [11,12]. High level expression of gp96 could contribute to tumorigenicity of certain tumors [12,22]. Recent studies have shown that HSP72 and gp96 are highly expressed in cancer tissues and have been verified to be associated with the development and progression of some tumors, such as hepatocellular carcinoma, gastric cancers, colonic tumors, breast cancers, lung cancers and so on, which have been used as prognostic markers in the above-mentioned carcinomas [8–14]. Although HSP72 and gp96 were highly expressed when gastrointestinal carcinomas progressed, but their roles in these carcinomas are not clear. It is reasonable to propose that HSP72 and gp96 up-regulation in these tumor cells are closely related with tumor cell survival and proliferation. Recent studies have suggested that HSPs take part in cell growth and proliferation in several ways such as signal transduction and cell cycle regulation through combining certain proto-oncogene products. This indicates that these proliferating cells need a higher level of HSPs to maintain the stability of tumor proteome [23,24]. It is believed that tumor cells are a group of highly proliferative heterogeneous cells which progress gradually through mutant oncogene products [25,26]. Continuous expression of HSPs in tumor cells may be required to serve as molecular chaperones in regulating and stabilizing these products during tumor growth process. At the same time, the existence of mutant or oncogene products may stimulate HSP synthesis [6,7,27–29].

Recent studies further supported the clinical significance of HSP72 and gp96 expression in the progression of gastrointestinal carcinomas. HSP72 and gp96 expression were found to be associated with important clinicopathological characteristics for patients' management. Consistently, HSP72 and gp96 expression were significantly associated with the presence of tumor size, lymph node and organ metastasis. In our previous studies, we found that over-expression of HSP70, HSP72, grp94 or gp96 in human gastrointestinal carcinomas had some relationship with progression, invasion and metastasis of the tumors [11–14,30–32]. Other researchers' studies [33–35] also showed that over-expression of HSP70 was related to tumor configuration, lymph node metastasis, and lymphatic vessel invasion in human gastrointestinal carcinomas. The studies found that histopathological differentiation was significantly correlated with the expression of HSP70, while there was no significant association between HSP70 expression and patient survival. Studies showed that not only was the expression of both HSP72 and gp96 in primary gastrointestinal carcinomas higher than the tissues adjacent to cancers, but also the expression of both HSP72 and gp96 in the carcinomas with metastasis was definitely higher than the carcinomas without metastasis. The level of HSP72 and gp96 expression in gastrointestinal carcinomas was related with the differentiated tissue type of cancers [30–32]. The results indicate that up-regulation of HSP72 and gp96 is likely to have some relationship with progression, invasion and metastasis of gastrointestinal carcinomas. The expression level of HSP72 and gp96 may be useful as diagnostic or prognostic markers for gastrointestinal carcinomas.

3. The chaperoned function of HSP72 in gastrointestinal cancers

HSPs, are thought to act as molecular chaperone, helping to transport, fold and process their target proteins. Although the cellular distribution of the increased heat shock proteins is unknown, it may be expected that each reaction would enhance the capacity of the pathway(s) in which heat shock proteins are likely to protect the associated cellular compartments from damage via abnormal protein interactions. Studies revealed that considerable expression of HSPs was found in tumor cells, indicating that HSPs may be induced by other stresses and participate in broader array of defenses during tumor cell growth and differentiation [5–7]. Thus, it may be presumed that under various stimuli and stressful conditions, in order to avoid the damage caused by deleterious factors such as nitrosamines, methylcholanthrene, hepatitis B or C virus-oncogenesis evocator, gastrointestinal cells have to transcribe and translate high levels of HSPs for sustaining normal metabolism and functions of cells. Under these conditions, gastrointestinal cells should synthesize HSPs rapidly to exert a protective role for the cells. The progression of gastroenterological carcinomas is a gradual process under the long-term influence of various stimuli. During the process, inducible HSP synthesis increases gradually [36].

Alpha-fetoprotein (AFP) always accompanies the development of liver cells, and it is possible that AFP may be related to the proliferation of tumor or fetal cells [37–39]. The mechanism for growth-promoting activity of AFP is still unclear, but escaping from the surveillance of the immune system is the primary cause for malignant growth of hepatocarcinoma cells [40,41]. Several investigations have shown that AFP could be individually synergized with other growth factors to promote the growth of many tumor cells [42,43]. AFP receptors have been found anchoring on the membrane of various tumor cells [44–46]. The receptor may mediate intercellular signal transduction which probably influences the expression of genes related to proliferation [44,45]. AFP can stimulate the expression of some oncogenes which may control cell cycle and enhance the proliferation of human hepatocellular carcinoma [47,48]. When BEL-7402 cell line was treated with AFP, oncogene proteins, such as c-fos, c-jun, n-ras and mutative p53 and $p21^{ras}$, increased rapidly, which play important roles in modulating growth and differentiation of the cells [49].

Enhanced expression of HSPs during the progression of cancer cells implies its close relationship with the cell growth [6–8]. It is interesting to note that AFP plays some roles during tumor cell survival and proliferation [37–39]. Recent studies have suggested a possible