

The Molecular Alterations Regarding Apoptosis in Hepatocellular Carcinoma Cells at a Glance

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Abstract

Ranking one of the most critical worldwide health troubles relating to mortality, hepatocellular carcinoma (HCC) has been a grievous scourge of humanity for a long time. Despite that plentiful attempts have been made, it still remains being a great challenge for us to conquer this disease. Multiple molecular alterations can be frequently detected in the pathogenesis and development of HCC, such as members of Ras family, Bcl-2 family and tumor suppressors. Importantly, most of these alterations are responsible for disrupting the balance between cell proliferation and apoptosis, which has been generally voted as a key event closely associated with carcinogenesis. Hence, this review aims to update the current related articles and provide a further understanding about such molecular changes relevant to trigger imbalances in the regulation of apoptosis in HCC.

Keywords: Hepatocellular carcinoma (HCC); Apoptosis; p53; Ras family; Fas/FasL; Survivin; Bcl-2 family; TNF- α

Introduction

Apoptosis, an autonomic ordered programmed cell death, is generally considered to be of great magnitude both in the modulation of growth and differentiation of normal cells and in ablating damaged, neoplastic cells and defending against pathogenic infections [1]. Carcinogenesis and tumor may arise when the homeostatic balance between cell survival and apoptosis is disrupted [2-4].

Being the fifth most common malignancy worldwide, hepatocellular carcinoma (HCC) is a major threat to human being [5,6]. Up to date, mountains of researches strongly suggest that HCC is highly resistant to traditional systemic therapies, at least partially owing to insufficient apoptosis [7-9]. Like many other tumors, HCC cells seem to be incapable of inducing their own deaths through apoptotic pathway, mutant p53 can be frequently accumulated at a fairly high level in HCC, which probably endow malignant cells with the ability to counteract the effect of multiple anticancer drugs. Molecular alterations in the RAS/ERKs pathway in HCC cells might contribute a lot to the undesirable resistance to apoptotic stimuli. Many HCC cells also show to be less sensitive to apoptotic signals induced by death receptor ligands, such as FasL. Moreover, some anti-apoptosis proteins such as Survivin, Bcl-xL, Mcl-1, and Bcl-2 are over expressed in HCC. The goal of this article is to focus on the related researches during the last few years and seek for a better understanding of these major molecular changes closely involved in the disturbance of apoptosis in HCC (Figure 1).

p53 and its alterations

Among the most crucial alterations observed in HCC, somatic mutations in *TP53* have been supposed to be correlated with the initiation and progression of this disease [10-12]. Wild-type (WT) p53 is normally expressed at a low level in the cells and can be activated rapidly upon multitudinous intrinsic and extrinsic stresses signals including DNA damage, osmotic shock, ribonucleotide depletion, etc [13]. Once activated, a cell cycle arrest could be induced to allow for DNA repair. Activation of p53 can also initiate cell apoptosis if damages show to be severe and irreversible. Such mechanism is important for body to maintain internal homeostasis.

However, when mutation occurs, the alternated p53 seemingly be able to discard the tumor-suppressing functions. Further studies have speculated that mutant p53 may grant the ability of escaping from apoptosis on malignant cells through redox mechanisms, such mechanisms are critical for the survival of hepatocytes during transformation and tumor progression [14]. Another possibility is that mutant p53 may form the complexes with isoforms of p63 and/or p73, inhibiting the biological functions of p63 and p73 [15]. Since currently several chemotherapeutic agents require p53 to induce apoptosis, disruption in the p53 pathway may finally lead to drug resistance. For these reasons, exploration of a way to reactivate and/or repair p53 and re-induce apoptosis in response to DNA damage by chemotherapeutic drugs may be a hopeful therapeutic strategy for HCC treatment [16-18]. Enormous efforts have been put into this field over the past few years. Some researchers pointed out that arterial administration of p53 products or adenoviral delivery of p53 recombinant DNA in mice models bearing HCC did not distinctly inhibit tumor growth [19], whereas thanks for DePinho and his partners' work [20], we have gradually realized that the effect of p53 deletion in HCC mostly depends on the concrete cellular micro-environment, especially telomeres are intact or dysfunctional. Data obtained from the related studies give us a stark indication that functional ablation of p53 protein might contribute a lot to hepatoma cell survival in the context of telomere-induced chromosomal instability [21].

Ras proteins and related effectors

In recent years, the Ras family have been attractive focuses of

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intense studies, in large part due to their vital roles in many carcinomas, HCC certainly no exception [22-24]. Being a prototypical member of the Ras superfamily (more than one hundred members), the Ras family show to be critical in modulating diverse range of cell behaviors, such as cell adhesion, migration, proliferation, differentiation, and apoptosis [25,26].

Though extensive researches reveal that point mutations of *ras* oncogenes seem to be quite common in a wide variety of tumors, the probability of these events is rare in HCC [27,28]. Further studies indicate that it is not mutation of *ras* genes themselves but a series of molecular alterations brought about by aberrant Ras activation in the Ras pathway that are closely related to the occurrence and development of HCC [27,29]. In the cause of this disease, up-regulated of H-ras (one of the most notable proto-oncogenes of the Ras family, owing the potential to cause normal cells to become cancerous when mutated) can be detected throughout different stages of tumourigenesis, followed by a discovery of the overexpressed B-raf (a protein belonging to the Raf kinase family of serine/threonine-specific protein kinases, which plays a role in regulating the MAP kinase/ERKs signaling pathway) in advanced period (Figure 1) [27,29,30]. These misadjusted proteins not only bring on increased invasion and metastasis but show to markedly disturb the normal apoptotic signal transductions. Besides, the functional loss of NORE1A, NORE1B and RASSF1A, some related effectors in the Ras-mediated pro-apoptotic pathway, can be frequently observed in HCC [27,32-36]. Since ongoing studies widely imply that these NORE1A, NORE1B and RASSF1A are the novel tumor suppressors and may act together to inhibit the mitogenic stimulation induced by Ras promoting apoptosis through activation of MST1 kinase [33-36], dysfunction of them might contribute a lot to undesirable proliferation as well as malignant transformation of hepatocytes.

Fas and FasL

Known as a major pathway for the induction of apoptosis in cells [37,38], the Fas-FasL system has been studied passionately for a long span of time. The cross-linking of Fas with FasL leads FADD (Fas-associated protein with death domain) to bind with the death domain of Fas, followed by the formation of a complex protein called death inducing signaling complex (DISC) and a direct recruitment and autocatalytic activation of pro-caspase-8 (and -10). Within this complex, the activation of pro-caspases can be inhibited by a cellular protein, FLICE-inhibitory protein (cFLIP). A sequence of biochemical cascade reactions result in multiple hallmarks of apoptosis including DNA degradation, cytomembrane blebbing, etc. In the upshot, Fas-bearing cells undergo apoptosis (Figure 1) [39]. This mechanism is of great significance not only in immune homeostasis, but also in wiping out cancerous cells [40,41].

Unfortunately, HCC cells as well as majority of other tumor cells seem to be relatively resistant to Fas/FasL-mediated apoptosis [42]. Since Fas/FasL system is a crucial apoptotic signal pathway in the liver, resistance to it may be greatly associated with the evasion of immune surveillance and tumor progression.

In the past few years, large efforts have been made to elucidate the possible mechanisms of this resistance. Many studies have shown that the majority of the HCC cells coexpress Fas and FasL, but all HCCs show one or more alterations in the Fas-FasL pathway [43]. The decreased expression level of Fas and/or downstream molecules, such as FADD, accompanied by the up-regulation of some molecules known to inhibit the Fas-mediated apoptosis such as soluble Fas (sFas) and Fas-associated phosphatase-1 (FAP-1) can be frequently detected in HCC [42,44]. These accumulating findings strongly imply that the

molecular alterations in the Fas/FasL pathway might enable hepatoma cells to escape from apoptosis. Therefore, it at least partially has to do with the pathogenesis of HCC.

However, despite that Fas/FasL system has been well studied after years of painstaking research and impressive results are already obtained in animal models, the clinical use of them for cancer treatment is still being a limitation given the potential severe toxicity [45,46]. But anyhow, involvement of this system leastways gives us a better understanding of the progression and development of HCC and one day people would hit on an ideal therapeutic regimen based on reinforcing Fas/FasL interaction or the apoptotic pathway.

Survivin and its dark side

Survivin is a recently described member of the inhibitor of apoptosis protein (IAP) family whose gene is ranked amongst the top five most tumor-specific genes in the human genome [47,48]. It is highly expressed during embryonic development but not in most adult tissues and cancer-adjacent normal tissues. However, when cancer occurs, significantly increased expression of Survivin could be obviously detected [49-51]. Up to now, a number of researches have been carried out to investigate the expression of Survivin and its relationship with apoptosis and proliferation in HCC. Homologous results show that there is a noticeable up-regulated expression of Survivin in HCC cells compared with that in adjacent cirrhosis tissues and normal tissues and increased protein expression level is markedly associated with the ratio of proliferative index to apoptotic index [52-54].

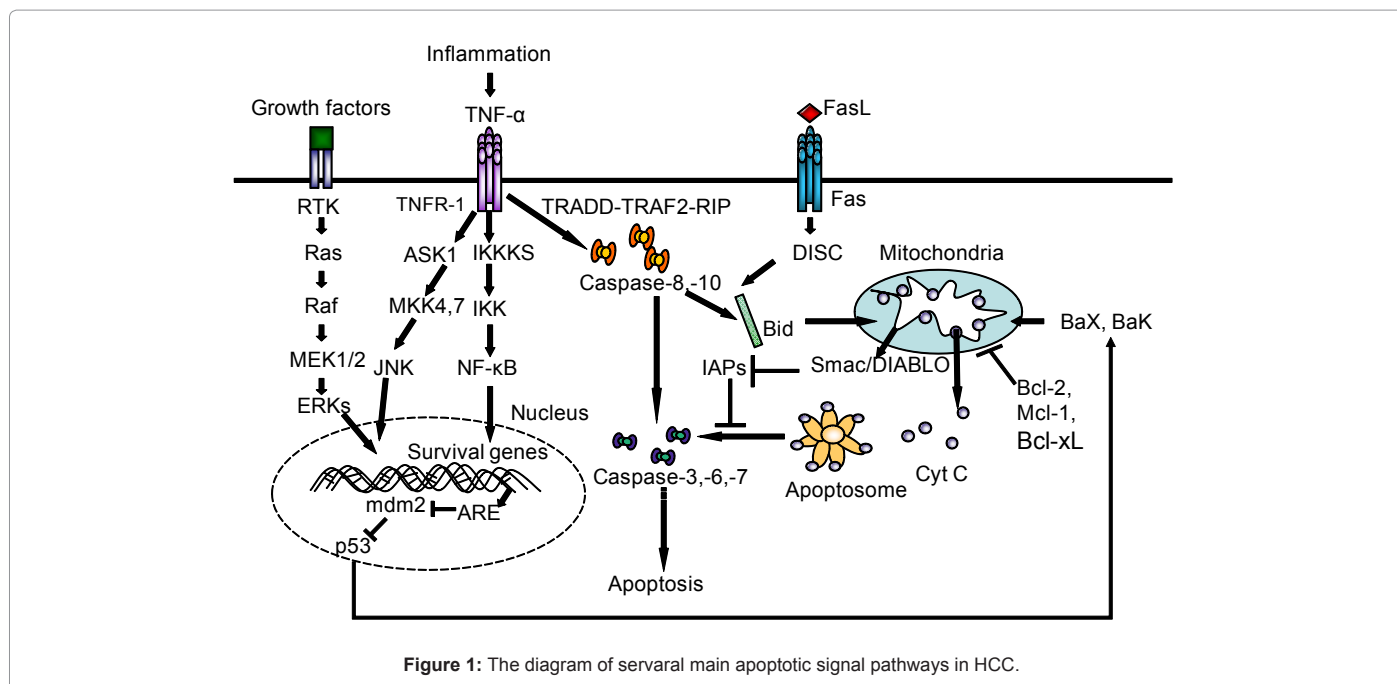
Analysis of the cell cycle after transfecting Survivin into hepatocellular carcinoma cells revealed that among all the tested cell lines, over expression of Survivin brought about a marked decline in G(0)/G(1) phase and an increase of S phase resulting in a growth dominance for cancer cells [55]. Thus together with the finding that knockdown the expression of Survivin by RNAi remarkably induces apoptosis and inhibits proliferation in HCC cells [56], which gives us an explicit enlightenment that this protein is positively associated with anti-apoptosis in HCC.

Objective researches implicate that Survivin protein can function as a dominant regulator of cell death and proliferation, controlling cell apoptosis through physically binding to downstream caspase-3 and caspase-7, and then inhibit activation of these proteins and/or act somewhere downstream of Bax and Fas-induced apoptosis signaling pathways to block Bax and Fas-induced apoptosis. This step can be suppressed by the X-linked IAP (XIAP) antagonist, Smac/DIABLO, which is released from the mitochondria and can relieve this inhibition and allow for apoptosis to proceed (Figure 1) [51,52]. Accordingly, thus it is reasonable to hypothesize that the over expression of Survivin is at least partially responsible for that malignant cells are able to escape from apoptosis and proliferate in a rapid manner.

Even though more works are still required to make clear about how Survivin produces its effects in the complicated process of cell apoptosis, at least we have realized its causal role in tumorigenesis.

Bcl-2 proteins

Among multitudinous regulators of internal apoptotic pathway known to date, an important family can never be overlooked. Comprised by more than 20 leaguers, the B cell lymphoma 2 (Bcl-2) family have been identified to be crucial to adjust cell apoptosis and promote normal growth [57]. Based on the number of Bcl-2 homology (BH) domains they contain, this family can be grouped into three sub-families. The first sub-family includes the anti-apoptotic multi-



domain proteins Bcl-2, Bcl-xL, myeloid cell leukemia-1 (Mcl-1), etc, characterized by containing four Bcl-2 homology (BH) domains with a hydrophobic binding cleft formed by domains 1-3 or three BH1-BH3 domains and a BH4-like helix. The next two groups show to be pro-apoptotic sharing three BH (BH1-3) domains, such as BAX (Bcl-2 associated X protein), BAK (Bcl-2 antagonistic killer), or only the BH3 domain, such as Bim (Bcl-2-interacting mediator of cell death), Bid (BH3-interacting-domain death agonist), and Bad (Bcl-2-associated death promoter). These proteins might exert their pro- or anti-apoptotic effects via governing the activation/inactivation of the mitochondrial permeability transition pore (MPTP) [58,59]. For instance, anti-apoptotic multidomain proteins could prevent the activation of MPTP and cytochrome c release, thus preventing downstream effectors activation and cell apoptosis. On the other hand, pro-apoptotic multidomain proteins can be activated by BH3-only proteins, which display sequence homology only with the BH3 domain and act as the sensors of the death signal, triggering the activation of MPTP and the subsequent release of cytochrome c. Then released cytochrome c might engender activation of a whole string of downstream molecules, such as caspase-3 and caspase-9. Once there, targeted cells are difficult to escape from dismantlement (Figure 1) [59-61].

At present, a smart few works have emerged the Bcl-2 family as a dominant factor relating to genesis and progression of many tumors [62,63]. In HCC, members of the family usually show to be maladjusted [64,65]. Take Bcl-2 as example, being the founding member of anti-apoptotic proteins in the family, Bcl-2 is frequently detected to be over expressed in the disease progression. Similar cases can be seen in its siblings including Bcl-xL and Mcl-1 [66-68]. At the same time, expressions of some pro-apoptotic proteins appear to be down-regulated, such as Bax and Bid [60,69]. Together, these findings demonstrate that Bcl-2 family might be another attractive and coming subject of researches about HCC.

TNF-α

A growing body of epidemiological and clinical data supports the concept that there is a causal relationship between inflammation

and cancer [70,71]. As persistent exposure to a wide variety of risk factors (hepatitis viruses, intermediates of alcohol metabolism, drugs, etc) could elicit the cellular immune response infection, so chronic inflammation may have a causative role in hepatocarcinogenesis [71,72]. More and more inflammatory cytokines have been received considerable interest, among which tumour necrosis factor-α (TNF-α) is the especially noteworthy one.

Being expressed by diverse kinds of cells comprising activated macrophages, NK-cells, T-lymphocytes, keratinocytes, neutrophils, and tumor cells, TNF-α is a well characterized cytokine with a vital role in wide-ranging biological effects [73]. It could exert the biological functions by binding two homotrimeric receptors, TNF-receptor 1 (TNF-R1) and TNF-R2. Binding of TNF to TNF-R1 results in the release of the inhibitory protein silencer of death domains (SODD) from TNF-R1's intracellular domain and the recruitment of the death domain-containing adapter protein TRADD (TNF receptor associated death domain) with the death domain-containing serine-threo-nine kinase RIP (receptor interacting protein), followed by an indirect recruitment of TNF-R2 in the TNF-R1 signaling complex and the activation of complex downstream signaling pathways, such as nuclear factor κB (NF-κB), c-Jun N-terminal kinase (JNK), and caspase [74,75]. Transformed hepatocytes seem to disturb such signaling and breakdown the liver homeostasis. Data from Knight B et al in 2000 suggested that TNF signaling was involved in the proliferation of hepatic stem cells during the preneoplastic phase of hepatocarcinogenesis and that loss of this signaling reduced the incidence of tumor formation in the TNF-R1 knockout mice model [76], and therefore TNF-α might provide a molecular bridge between inflammation and cancer. Despite that much work is required to reduce the toxicity for systematic administration, TNF-α still shows the potential to be a cancer therapeutic during the early stages of liver carcinogenesis.

Conclusions

In summary, overwhelming evidence has strongly suggested that there is a close association between dysregulation of cell apoptosis and the pathogenesis of HCC. Failure of apoptosis might allow the survival

of malignant cells, thus being liable to interrupt the normal growth. Notwithstanding that lots of risk factors related to HCC have been well studied, a jillion relevant molecular alterations compromising the balance between HCC cell death and survival are still needed further research. A better understanding of them is required for the development of optimal apoptosis-targeted treatment strategies. Taken altogether, over-activation of anti-apoptotic signals and inhibition of pro-apoptotic molecules can be frequently observed in this annoying disease. Regulation of these dysfunctional signals of apoptosis in HCC may consider as the choice for treatment of HCC. Although there is much work to be done still and no efficient method existed at present, no one doubts that success is on the way.

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