Resveratrol inhibits epithelial-mesenchymal transition in hepatocellular carcinoma

Asmaa M.A. Bayoumi1#, Esraa M.M.A. Khalifa1*, Mohamed M. Sayed-Ahmed2, Marwa Sharaky2 and Maiiada H. Nazmy1

1 Department of Biochemistry, Faculty of Pharmacy, Minia University, Minia 61519, Egypt.
2 Pharmacology and Experimental Oncology Unit, National Cancer Institute, Cairo University, Cairo 11796, Egypt.

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Abstract

Hepatocellular carcinoma [HCC] is a brutally aggressive cancer that puts a tremendous amount of strain on both the medical systems and the drug regulatory organizations as well. It is believed that a crucial stage in the development of HCC is the epithelial-mesenchymal transition [EMT], which increases hepatocyte malignancy and is linked to invasion and metastasis. Resveratrol [RES] has been shown to reverse EMT in a number of cancer types. In order to further understand how RES influences EMT in HCC, we have chosen to concentrate on studying and summarizing the serine/threonine kinase [Akt]/glycogen synthesis kinase 3-beta [GSK3β]/Snail signaling pathway as one of the central pathways involved in activating EMT and tumorigenesis in this review.

Keywords

Hepatocellular carcinoma; epithelial-mesenchymal transition; resveratrol; Akt/GSK3β/Snail pathway

1. Introduction

Being the third most common cause of cancer-related deaths worldwide and the fifth most common cancer, hepatocellular carcinoma [HCC] is a significant health burden. In 2020, about 19 million new cancer cases were detected and almost 10 million cancer fatalities were reported [1-3]. Although hepatitis B and C virus-related underlying infections account for the majority of HCC cases [4, 5], other risk factors like alcohol abuse, obesity, and environmental variables also play a role in the disease etiology. Among the major environmental variables that cause HCC is diethylnitrosamine [DEN], which is present in tobacco smoke, alcoholic beverages, occupational settings, agriculture chemicals and pharmaceutical products [6]. In addition to initiation of oxidative stress, DEN has also been found to be the primary cause of DNA damage that not only induces liver cell mutations, but also promotes postnecrotic hepatocellular proliferation [7, 8]. Given these conditions, DEN is a widely used model for HCC in animals such as rats and mice, that mimics the symptoms agonizing human beings [9, 10].

The genetic controls and biochemical mechanisms underlying the pathophysiology of HCC have been areas of intensive research [11, 12]. In many of these studies, activation of epithelial-mesenchymal transition [EMT] program has been suggested as the mechanism linked to acquisition of invasive phenotype and the subsequent systemic dissemination of the epithelial cancer cells [13]. Due to the high recurrence rates and development of adverse effects after therapy, as well as the fact that liver cancer is typically discovered at an advanced stage since the lack of symptoms during early stages of the disease, the current management of HCC is not satisfactory [14, 15]. Recently, a considerable attention has been paid to the use of natural polyphenols as a prophylactic and therapeutic remedy for liver cancer. They are multi-targeting, less expensive, and prevalent in whole foods with minimal to no negative effects [16, 17]. In this review, we provide a summary on the role of EMT in the different aspects of HCC and we suggest that targeting of EMT may pave the way to develop efficacious and safe therapies to overcome the disease.

2. BASIC CONCEPT OF EMT

Epithelial to mesenchymal transition [EMT] is the process during which, the epithelial cells miss their biosignatures and display mesenchymal cell phenotypic characteristics [18-22]. This is manifested by the loss of cell polarity, acquisition of invasive and migratory qualities and resistance to apoptosis [23]. An assortment of genetic and epigenetic alterations mediate both EMT and its opposite mesenchymal to epithelial to transition [MET] that are physiologically noticed during organ development and wound healing and are pathologically associated with tumor invasion and dissemination [24-26].

Activation of EMT is driven by a series of transcription factors [EMT-TFs] including members of the SNAIL, TWIST, and ZEB families restricting the formation of E-cadherin [27-30]. Transforming growth factor-beta [TGFβ], released by a variety of cell types in the tumor-associated stroma, is regarded as the primary inductor of EMT [31, 32]. TGFβ was found to have a dual role in tumor progression; in the early stages, TGFβ has an anti-tumorigenic impact increasing apoptosis and decreasing the growth whereas in the advanced stages, TGFβ has a protumorigenic impact inducing EMT and boosting metastasis [33, 34].
34]. It exerts its effect via a combination of Smad-dependent and -independent mechanisms. Dependent of Smad activity, TjRs-mediated phosphorylation of R Smads fosters the production of high-mobility group A2 [HMGA2] to upregulate SNAIL1 transcription [35]. Independent of Smad activity, TjRII-mediated phosphorylation of Par6 promotes the dissociation of cell junction complexes [36]. Moreover, TGFβ acts in a context specific manner in co-operation with other pathways, including Hippo, WNT/β-catenin, mitogen-activated protein kinase [MAPK]/extracellular signal-regulated kinase [ERK], and phosphoinositide 3-kinase [PI3K]/Akt to enhance their functions [37-39].

3. EMT IN HCC: Akt/GSK3β/SNAIL PATHWAY

A previous work has established the crucial role of the Akt/GSK3β/Snail signaling pathway in hepatocarcinogenesis and EMT [40-43]. The serine/threonine kinase [Akt] is an important signaling kinase participating in a wide range of physiological and pathological processes including angiogenesis and cancer progression [44, 45], and is fundamentally linked to the initiation of EMT [Figure 1] [41, 46]. According to Alessi et al. [1996] [47], Akt activity depends on Ser473 phosphorylation. After being phosphorylated, Akt serves to inhibit particular enzymes by phosphorylation such as glycogen synthesis kinase3-β [GSK3β] [48-50]. GSK3β is a multitasking kinase engaged in many signaling pathways and biochemical attributes such as neurologic disorders, diabetes, and cancer. Phosphorylation of GSK3β occurs at two key regulatory sites, Tyr216 indicating its activation and Ser9 indicating its inactivation. Akt/GSK3β phosphorylates SNAIL leading to its inhibition by ubiquitination and degradation, while P-GSK3β leads to its stabilization and nuclear localization, ensuing induction of EMT [51-53]. SNAIL has been implicated in various developmental cell fate and cell survival processes and has been correlated with recurrence and poor prognosis in various tumors [54, 55]. It moves back and forth between the cytoplasm and nucleus, where it attaches to an E-box site in the promoter of the gene that codes for E-cadherin [56], prevents the transcription of E-cadherin and therefore leads to EMT [57-59]. It also controls a number of other EMT phenotypic traits including; increased expression of mesenchymal cell markers [vimentin, N-cadherin and fibronectin], decreased expression of epithelial markers [claudins, occludins and cytokeratins], obstruction of proliferation and protection from cell death [60]. Accordingly, blockade of Akt/GSK3β/SNAIL pathway could be a promising strategy, which aims at protecting hepatocytes from EMT, thus controlling HCC.

4. THERAPEUTIC INTERVENTIONS

Of the various phytochemicals tested for their beneficial health effects, resveratrol [RES] has drawn much attention [61-63]. Many plants, including grapes, mulberries and peanuts, produce RES in reaction to harmful circumstances like stress, UV irradiation, and fungal diseases [64-66]. Several studies have indicated that, mechanisms underlying the hepatoprotective potential of RES may be combinations of anti-oxidant, anti-inflammatory, antimutagenic, reversal of EMT, influence on the cell cycle and cell differentiation, induction of apoptosis and suppression of proliferation playing roles in the initiation and secondary modification stages of neoplastic development [67-72]. RES was able to suppress chemical-induced carcinogenesis, relying on its inhibitory action of CYP450 dependent oxidase detoxification and elimination by up-regulating catalase and superoxide dismutase activities [73, 74]. Besides, a previous study has evaluated the important role of RES in hindering the TGFβ /Smads signaling pathway and reducing the rate of lung and hepatic metastases in mice in an orthotopic mouse model of colorectal carcinoma [63]. In addition, RES blocked EMT, invasiveness and metastatic capacity of head and neck cancer cells by suppressing the expression of the EMT-related genes SLUG, ZEB1, E- and N-cadherin [75]. Similarly, RES prevented EMT that had been induced by the transcription factors SNAI1 and TWIST1 and also prevented the WNT/β-catenin signaling pathway in glioma stem cells [76, 77]. Furthermore, RES was found to induce apoptosis in MOLT-4 cells by suppressing the NOTCH signaling pathway [78, 79]. Thus, in light of available experimental data, RES represents an impressive candidate with many benefits hoping to be used either alone or in combination with chemotherapy in the management of HCC.

5. CONCLUSIONS

Herein, we presented an overview of the possible targets contributed to HCC prevention. We also highlighted the potential of RES against HCC through blocking of the Akt/GSK3β/Snail signaling and suppression of EMT. Future studies are mandatory to uncover the diversity of signaling pathways enforcing EMT programs during HCC and to evaluate the possibility of applying RES to patients at high risk of developing the disease [80, 81].

REFERENCES


