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AQP3,5 and NF-κB regulation by EGCG in oral cancer, one of possible mechanism

Regulacja AQP3,5 i NF-κB przez EGCG w raku jamy ustnej, jeden z możliwych mechanizmów

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ABSTRACT

Aquaporins (AQPs) are membrane proteins involved in controlling passage of water between into and out of cells, and in the mechanism of tumor cell migration and proliferation by promoting cell adhesion and facilitating glycerol uptake. AQP5 and AQP3 expression are associated with several oral cancers and are linked to tumor growth development and metastasis. Nuclear factor kappa B (NF-κB) plays a central role in many signal transduction pathways and is associated with tumor development. AQP3 and AQP5 regulation by NF-κB suggested that it may be a potential therapeutic target for the treatment of cancer. EGCG inhibits proliferation and induce apoptosis in oral cancer. In this review we aim to discuss the possible mechanisms of EGCG interaction with AQP5, AQP3 and NF-κB in oral cancer.

Keywords: green tea, cancer, aquaporins.

STRESZCZENIE

Akwaporyny (AQP) to białka błonowe biorące udział w kontrolowaniu przepływu wody między komórkami i poza komórkami oraz w mechanizmie migracji i proliferacji komórek nowotworowych poprzez promowanie adhezji komórek i ułatwianie wychwytu glicerolu. Ekspresja AQP5 i AQP3 jest związana z kilkoma nowotworami jamy ustnej oraz z rozwojem nowotworu i przerzutami. Czynnik jądrowy kappa B (NF-κB) odgrywa kluczową rolę w wielu szlakach transdukcji sygnału i jest związany z rozwojem nowotworu. Regulacja AQP3 i AQP5 przez NF-κB sugeruje, że może to być potencjalny mechanizm terapeutyczny w leczeniu raka. EGCG hamuje proliferację i indukuje apoptozę w raku jamy ustnej. W publikacji omówiono możliwe mechanizmy interakcji EGCG z AQP5, AQP3 i NF-κB w raku jamy ustnej.

Słowa kluczowe: zielona herbata, rak, akwaporyny.

Introduction

Oral cancer development is connected with smoking of cigarettes, drinking of alcohol, bad oral hygiene, periodontal diseases and diet. It manifests in elder people, especially in man. However, last decade indicates the higher ratio of oral cancer cases in younger people, what is probably connected with human papilloma virus (HPV) infection. Oral cavity is an open environment constantly exposed on microbiome, changing of temperature and different pH.

There is indicated that some of pathogens, especially capable of tissue invading, influence on apoptosis via nuclear factor kappa B (NF-κB) [1]. From the other hand natural antioxidants can inhibit the (NF-κB) way [2].

Aquaporins (AQPs)

Aquaporins (AQPs) play a major physiological role in controlling the passage of water between different organellum or cells and are involved in many biological functions such as cancer and deficient secretion of saliva due to glandular dysfunction [3, 4]. It has been reported that the increased expression of AQPs is closely associated with tumor growth, development, invasion and metastasis which may be therapeutic targets in cancer therapy [5]. It has been shown that suppression of

AQP1 expression in lung adenocarcinoma can inhibit tumor cell invasion, indicating the therapeutic potential of this protein in lung cancer [5]. Other AQPs have been reported in several types of cancers. Studies have shown that AQP5 is expressed in gastric, lung, ovarian, pancreatic and colorectal cancer. Other studies have reported that AQP5 and AQP3 are expressed in several oral cancers and that AQP3 may play a major role in squamous cell carcinoma (SCC) growth in tongue and esophageal cancers [6, 7].

The suggested molecular mechanism is that polarization of AQPs can induce changes in the shape and volume of migrating cells. AQPs can be involved in cell migration by two mechanisms: By moving to the front ends of migrating cells to induce a rapid flow of transmembrane water due to changes in osmolarity produced by transmembrane ion flow and actin depolarization. They can be involved also by inducing a rapid change in the volume of migrating cells to the extracellular space due to the rapid change in transmembrane water flow [8]. In addition, transmembrane water transport promotes lamellipod formation and stability through actin polymerization [9, 10]. Lamellipodia along with filopodia and invadopodia play a major role in cell migration. Lamellipodia are large, flat, actin-rich protrusions that extend in the direction of locomotion and provide a base on which the cell advances [11]. During protrusion formation, the localization of AQPs at the leading edges of migrating cells facilitates cell volume changes and cytoskeletal modifications [12–16]. It has also been proposed that AQP1 promotes lamellipod formation [17–19]. AQPs may also be involved in the mechanism of tumor cell migration and proliferation by promoting cell adhesion and facilitating glycerol uptake [9, 10]. It has also been shown that AQPs can induce transcription of genes involved in cell growth, transformation and survival [9, 10]. Recently it has also been suggested that certain AQP isoforms are capable of absorbing hydrogen peroxide and may promote tumor progression [20–22].

Kusayama et al. [7] studied the expression of AQP3 in oral SCC and its role in cell adhesion and cell growth in tumor tissue. They found that the expression is significantly higher in tumor cells compared to non-tumor tissue. They also demonstrated that inhibition of AQP3 by interfering RNA (siRNA) induced inhibition of the focal adhesion kinase and protein kinase (MAPK) signaling pathway. This inhibition affects cell adhesion and growth by inhibiting α5 and β1 integrins [7].

Another study has shown that the expression of AQP5 and AQP3 in tumor tissues and cell lines of SCCs is significantly higher compared to non-tumorous ones. This expression was also found in non-tumoral areas of malignant salivary gland tumors. AQP5-siRNA and pan-AQP inhibitors such as CuSO4 were used to determine the role of AQP5 in cell growth of SCC cell lines (SAS, SCCKN and CA9-22). These inhibitors showed that suppression of cell growth of SAS cell lines by AQP5 knockdown is mediated by inhibition of integrins and the MAPK signaling pathway. In addition, the combination of AQP5-siRNA and AQP3-siRNA has been shown to also inhibit the growth of SCCs and there is no synergy between the two treatments on tumor growth suppression [6].

Matsuo and Kawano [23] have demonstrated that decreased expression of AQP3 correlates with lymph node metastasis in OSCC. Another study by Liu et al. indicated a correlation between overexpression of AQP3 and AQP5 and metastasis in patients with esophageal SCC [24].

It has been reported that lipopolysaccharide (LPS) decreases AQP5 mRNA expression via nuclear factor kappa B (NF-κB) and p-c-Jun/c-Fos in the parotid gland [25].

NF-κB is identified as an enhancer of the immunoglobulin j light chain gene in lymphocytes [26]. It plays a central role in many signal transduction pathways and is linked to tumor development, regulation of apoptosis and embryonic development [27]. It has been suggested that it may be a potential therapeutic target for the treatment of cancer [28].

Recently, a study has shown that NF-κB play a major role in the mechanism of intestine permeability alteration of irritable bowel syndrome (IBS) by regulating the expression of AQP1,3 and 8 [29]. Another study has shown that AQP3 facilitates H2O2 transport and is involved in NF-kB signaling in keratinocytes and in the development of psoriasis [30]. Which indicate that NF-kB might act as coordinator by regulating AQP3 and AQP5 in oral cancer development.

EGCG regulation in oral cancer

Several studies have shown that epigallocatechin-3-gallate (EGCG) has anticancer activity and can inhibit proliferation by inducing apoptosis [31] in multiple cancers [32, 33].

It has been reported that EGCG treatment of oral squamous cell carcinoma can suppress the viability of cancer cells. The author has also demonstrated that treatment induced G1 phase arrest of tumor cells and increased caspase-7 and 3 activi-

ties, as well as apoptotic cells compared to control cells [34].

The other mechanisms of EGCG in anticancer activity are needed.

Aquaporin expressions is associated with metastasis and angiogenesis and might playing a major role in the proliferation and division of cancer cells in the surrounding matrix [35,36]. AQP5 expression has been shown to be regulated by NF-κB [37,38] in ovarian cancer as well as ascites [39]. Yan et al. [39] have studied the effect of EGCG on the expression of AQP5 and NF-κB p65in cells of ovarian cancer cell line SKOV3. The author has shown that EGCG inhibited proliferation and induced apoptosis in SKOV3 ovarian cancer cells. He also demonstrated that treatment of cells with 40lg/ml EGCG decreased the expression of AQP5 and NF-κB p65 [40].

Conclusion

Collectively, it seems clear that the interaction between AQP5, AQP3 and NF-κB plays a major role in the development of several pathologies and types of cancer. Furthermore, the regulation of AQP5 and AQP3 by NF-κB could probably be one of the mechanisms by which EGCG induces the inhibition of cancer cell development in the mouth.

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Conflict of interest statement
The authors declare no conflict of interest.

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