IKKα functions as a tumor suppressor in epithelial-derived tumors through an NF-κB-independent pathway (Review)

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Abstract. Recent studies have shown that IkB kinase α (IKKα) plays an important role in human skin cancer and acts as a major regulator for keratinocyte terminal differentiation and proliferation. IKKα deficiency or mutation is associated with human tumor development; thus, overexpression of IKKα could prevent tumor progression. However, findings suggest that IKKα is equally essential for many other epithelial-derived tumors. In the present study, we discussed the role of IKKα as a tumor suppressor in IKKα-mediated epithelial-derived tumors and its activation pathway, which is different from the traditional NF-κB pathway. The present study provides theoretical basis for understanding the molecular mechanisms involved in IKKα-related tumors.

Contents

1. Introduction

2. Structure and traditional functions of IKKα

3. Role of IKKα in normal epithelial and skin squamous cell carcinoma (SCC)

4. The role of IKKα in lung SCC tumorigenesis

5. The novel role of IKKα in head and neck cancer

6. A different role of IKKα in hormone-related breast and prostate cancer

7. Conclusions

1. Introduction

Inactivation of tumor suppressor genes (TSGs), whose structural abnormalities and functional disorders lead to changes in their regulatory mechanism, plays an important role in the development and progression of human tumors. The role of TSGs involved in normal differentiation of tissues and inhibition of carcinoma has gained increasing attention (1,2). Numerous studies have shown that the mutations and/or deletions of IKKα frequently occur in human epithelial-derived carcinogenesis, while IKKα stable expression appears in corresponding normal tissues (3-6).

2. Structure and traditional functions of IKKα

IKKα is a 85-kDa polypeptide containing an amino-terminal serine-threonine kinase catalytic domain and carboxy-terminal helix-loop-helix (HLH) and leucine zipper-like (LZip) amphipathic α-helical domains (7,8). IKKα and IKKβ, which share similar substrate specificities as catalytic subunits, form a specific IkB kinase complex with the regulatory subunit IKKγ/NEMO, thus contributing to kinase activity regulation in the cytoplasm (9). A series of surrounding signals, such as aberrant cytokine production, integrins, growth factors and cytokine receptors activate the IKK complex for the phosphorylation and ubiquitylation of IkBs, resulting in subsequent proteasomal degradation of p105 to p50. This is the canonical NF-κB pathway (Fig. 1A), which leads to the nuclear entry of NF-κB/RelA (p50/p65) (10,11). IKKα also forms IKKα/IKKα homodimers to stimulate an alternative NF-κB pathway by transformation of NF-κB2/p100/RELB into p52/RELB heterodimers, which translocate into the nucleus and exert...
IKKα functions as a major regulator in keratinocyte proliferation and differentiation. Calcium (Ca²⁺) is essential for the induction and maintenance of the terminal differentiation status in the epidermis (14,15). However, primary cultured IKKα⁻/⁻ keratinocytes fail to undergo terminal differentiation, which is also not induced by Ca²⁺. Conversely, reintroduction of wild-type (WT) or kinase-inactivated IKKα induces terminal differentiation of keratinocytes, while this does not occur when IKKβ is reintroduced, even though it exhibits a similar structure and function with IKKα. Furthermore, compared to IKKβ in the cytoplasm exclusively, IKKα exists both in the cytoplasm and nucleus (4,16). IKKα shows nuclear localization in the normal epidermis of humans and mice (3,17). In the nucleus, IKKα does not exert kinase activity and has a special role different from that of IKKβ. Moreover, mutant IKKα is not only incapable of moving to the nucleus, but it also fails to induce terminal differentiation of IKKα⁻/⁻ keratinocytes (17). These findings indicate that nuclear IKKα regulates keratinocyte proliferation and Ca²⁺-dependent differentiation. However, how Ca²⁺ is involved in the process of IKKα-induced keratinocyte terminal differentiation remains to be determined.

Function of IKKα as a tumor suppressor in skin SCC. Studies have demonstrated that IKKα mutations are present in human SCC and that a marked reduction in IKKα expression occurs in poorly differentiated human and mouse cutaneous SCCs (18). In studies of chemical carcinogen-induced (19) or UVB-induced (20-22) skin carcinogenesis, the findings have shown that lack of IKKα expression promotes the development of skin papillomas and carcinomas in IKKα⁺/- mice. In chemical carcinogen-induced skin carcinogenesis, reduced levels of IKKα promote the oncogenic H-Ras pathway and enhance the mitogenic activity, extracellular signal-regulated kinase (ERK) activity and overexpression of growth factors (19); and in addition, influence UVB-related p53 mutations, upregulate the expression of monocyte chemoattractant protein-1 (MCP-1/CCL2), TNF-α, IL-1 and elevate macrophage migration, which are crucial for accelerating UVB skin carcinogenesis (21,23). In contrast, increased IKKα expression antagonizes mitogenesis.
and angiogenesis, thus antagonizing the development of malignant carcinomas and metastases (Fig. 2A).

Overall, IKKα plays an important role in skin cancer, and the maintenance of an adequate level of IKKα is essential for protecting the skin from various harmful stimulations and carcinogen attacks. It is necessary to investigate whether certain mutations in IKKα convert its function from a tumor suppressor to an oncogene.

**Mechanism of IKKα in IKKα-mediated skin tumorigenesis**

*The EGFR/ERK/EGF/HB-EGF/ADAM signaling pathway.*

Inactivation of epidermal growth factor receptor (EGFR) or reintroduction of IKKα or kinase-inactive IKKα represses DMBA-induced H-Ras mutations or TPA-induced excessive ERK activity or excessive expression of EGF and FGFs. Reduction in IKKα expression promotes expansion of cells carrying UVB-induced-p53 mutations and induces the recruitment of macrophages and inflammation by upregulating expression of cytokines and MCP-1/CCL2. In spontaneous carcinogenesis, IKKα suppresses the transcription of EGFR ligands and their ligand activators, resulting in inhibition of EGFR and ERK activities. IKKα cross-talks with EGFR, AP-1 and Stat3 pathways in a loop. Moreover, IKKα inhibits the TGF-β/Smad2/3/c-Myc pathway and contributes to the regulation of cyclin D1 in the G1/S and 14-3-3σ in the G2/M phase to maintain a normal balance in the cell cycle. In oral carcinoma, the genetic instability of IKKα and hypermethylation of its CpG islands causes some promoter hypermethylation and epigenetic inactivation of gene transcription. Reduced EZH2 inhibits H3K27 histone methylation on the IKKα promoter and relieves IKKα transcriptional repression. Overexpression of IKKα reduces CK13 and increase CK8 expression to induce epithelial differentiation. Through another manner, IKKα suppresses NPC through the ERK pathway by regulating MMP-9. IKKα is independent of the NF-κB pathway in the above process. In spontaneous lung SCCs, kinase-dead IKKα knock-in suppresses the expression of p63, Trim29, K5 and EGFR/ERK activity and CDK1, ROS1, IL-1 levels to keep balance between cell proliferation and differentiation and prevents an excessive inflammatory microenvironment. However, the increased canonical NF-κB pathway contributes to IKKα-related lung SCC development and this requires further elucidation.

The transforming growth factor β (TGF-β)/Smad2/3/c-Myc pathway. The transforming growth factor β (TGF-β)/Smad2/3 pathway is also important for skin homeostasis and skin tumor development (Fig. 2A). Upon treatment with TGF-β, IKKα forms a complex with Smad2 or Smad3 on the promoters of Mad genes (16,29). Studies have suggested that loss of IKKα downregulates Mad1, Mad2, Mad3, Mad4 and Ovol1 expression and increases
c-Myc activity, which is associated with cell differentiation in keratinocytes. Excessive c-Myc activity inhibits the prevention of cell cycle exit and cell apoptosis, thereby destroying regular cell differentiation. Moreover, a reduced level of Max/Mad dimers induces the competition with c-Myc, which can form dimers with Max as well, thus abnormally enhancing c-Myc/Max dimer-induced cell proliferation (30,31).

Although TGF-β acts as a tumor suppressor at the early stage of tumor development and affects cell proliferation, differentiation and inflammation (32), the levels of TGF-β are high in SCC. Accumulating evidence has revealed that TGF-β plays a bidirectional role in cancer progression (33,34). Studies suggest that TGF-β works as a tumor promoter by modifying tumor promoter-induced cell proliferation and inflammation, stimulating angiogenesis and promoting epithelial-mesenchymal transition (EMT) (35). In skin cancer, TGF-β fails to exert its tumor suppressor activity in IKKα-null or IKKα-mutated tumor cells, owing to the fact that IKKα is a major target of mutagenesis in tumorigenesis. Thus, IKKα is crucial for TGF-β-induced tumor suppressor activity during skin tumorigenesis.

The role of IKKα in the cell cycle
IKKα and cyclin D1. Several studies suggest that IKKα regulates the turnover and subcellular distribution of cyclin D1 by inducing its phosphorylation of cyclin D1 (36) (Fig. 2A). Cyclin D1 is an important regulator of cell-cycle initiation and G1/S transition. Cyclin D1 binds to Cdk4 and Cdk6 to form a pRB kinase, which phosphorylates and deactivates the tumor-suppressor protein pRB. Upon phosphorylation, pRB loses its repressive activity for the E2F transcription factor, which activates the transcription of several genes required for cell-cycle initiation and G1/S transition. Furthermore, overexpression of cyclin D1 plays a critical role in tumor development through stimulating various growth factors, such as anchorage-independent growth and vascular endothelial growth factor (VEGF) (37).

IKKα is critical for the phosphorylation of cyclin D1 at the T286 residue, which is indispensable for the transport of the protein out of the nucleus during the S phase of the cell cycle and for its degradation (38). IKKα-cells have cyclin D1 in the nucleus and therefore, abnormally activate CDK4/6 kinase activity and pRB phosphorylation, leading to the deregulation of the G1/S checkpoint. This process may be enhanced by the presence of cyclin D1 mutations (39); at the same time the T286 residue remains in the nucleus and promote tumorigenesis.

IKKα and 14-3-3σ. 14-3-3σ, as a G2/M cell cycle checkpoint, regulates the cell cycle and allows cells to repair genetic errors, thus preventing mutagenesis and genomic instability (40). It is specifically and highly expressed in keratinocytes and other epithelial cells. A large number of studies have shown that 14-3-3σ is silenced in many human epithelial cancer cells. Studies show that the level of 14-3-3σ is low in IKKα-cells but is restored after the reintroduction of IKKα (Fig. 2A). Furthermore, the protein is a downstream target of IKKα in the pathway of IKKα-mediated cell cycle regulation and functions in response to DNA damage (41,42).

Moreover, 14-3-3σ is also a target of IKKα for maintaining genomic stability. 14-3-3σ contains many CpG islands. Its hypermethylation and loss of final σ expression are the most consistent molecular alterations in malignancies. Studies have confirmed that 14-3-3σ CpG islands are hypermethylated in IKKα-c keratinocytes, which is associated with trimethyl-H3-K9, a protein essential to DNA methylation. An entire kinase domain (300 aa) deletion of IKKα does not permit IKKα to bind to the N-terminal tail of H3, which fails to prevent trimethylation of H3-K9 at the 14-3-3σ and fails to induce the expression of 14-3-3σ. Conversely, binding of IKKα to H3 probably prevents H3-K9 trimethylation, thereby shielding the 14-3-3σ locus from hypermethylation and maintaining genomic stability. Thus, IKKα plays an important role in epigenetic regulatory mechanisms of 14-3-3σ for cancer prevention (41). However, further studies may be necessary to unveil whether IKKα utilizes this mechanism to regulate a series of genes, providing the foundation for exploiting its hypermethylation as a marker for the early detection of malignancies.

Therefore, IKKα-mediated cell cycle regulation mechanism via cyclinD1 or 14-3-3σ is important for prevention of skin tumors.

4. The role of IKKα in lung SCC tumorigenesis

Studies have revealed a decrease in IKKα RNA expression level in human lung cancer cell lines (4). Recent findings have demonstrated the pivotal role of IKKα in the development of spontaneous lung SCC. Studies have established a kinase-dead IKKα knock-in (IKKαΔK44/A44, IKKαΔK44/K44) mouse model, in which the lysine (K) at amino acid 44, the ATP-binding site, was replaced with alanine (A), to develop spontaneous lung SCCs to determine the role of IKKα in normal bronchial epithelium and its related carcinomas. The mice did not display any obvious abnormalities at the time of birth, indicating that IKKα kinase inactivation does not affect mouse embryonic development. However, spontaneous lung tumors, whose weight was timely increased, appeared in IKKαK44/K44 mice from 4 to 10 months of age and the animals began to die after 6-10 months. In that case, IKKα levels in the lungs of IKKαK44/K44 newborns were low and markedly decreased at 4 months of age. Therefore, reduction in IKKα levels contributed to the development of spontaneous lung tumors. Furthermore, atypical squamous hyperplasia development in the fore-stomach, esophagus and skin was also investigated in the IKKα-deficient mice. However, reintroduction of the IKKα transgene prevented the development of the tumors (43). These results demonstrated that high levels of IKKα prevent lung tumor development.

Some studies suggest that lung SCCs are derived from keratin 5-positive (K5+) basal cells of the pseudostratified bronchial epithelium. K5+ epithelial cells lacking IKKα may be targets for SCC development (4,44). IKKαK44/K44 mice expressed high levels of K5, as well as transcription factor p63, tripartite motif-containing 29 (Trim29) proteins, and Ki67, which was similar to the expression profile in human lung SCCs (43).

p63, a member of the tumor suppressor p53 family, is required for the formation of the epidermis, other stratified epithelia and epithelial appendages (45). The N-terminal-truncated form of p63 (ΔNp63) is predominately expressed in the epidermis and is overexpressed in various epithelial cancers, where it exerts oncogenic activities (46). In addition,
Trim29 overexpression has been studied in human lung, bladder, colon, ovarian, endometrial and gastric cancers. In these cell types, Trim29 promotes cell proliferation and inhibits p53 activity (47,48). These findings highlighted that increased epithelial cell-specific p63 and Trim29 may contribute to lung SCC development. Compared to WT mice, ΔNp63 and Trim29 protein levels were increased in the lungs of IKKe^{KA/KA} mice and further increased in the lung affected by SCCs. Chromatin immunoprecipitation (ChIP) assay was used to explain how IKKα regulates the expression of both Trim29 and ΔNp63. The results showed that nuclear IKKα bound to the promoter regions of Trim29 and p63, which was associated with high levels of H3 lysine 27 trimethylation (H3K27me3), a negative transcription modifier and low levels of H3 lysine 4 trimethylation (H3K4me3), a positive transcription modifier, thus leading to the control of their expression. This process occurred both in human and mouse lung epithelial cells (43,49,50). In consequence, nuclear IKKα regulates the expression of both Trim29 and ΔNp63 at the transcription level by modifying the chromatin structure of Trim29 and p63 in an epigenetic manner to prevent tumor development (Fig. 2D).

In addition, the levels of insulin growth factor 1 (IGF-1), cyclin-dependent kinase 1 (CDK1) and the activities of EGFR, ERK and p38 were elevated in the lungs of IKKe^{KA/KA} mice and were considerably increased in SCC compared to WT lungs, which is similarly to human. Excessive inflammatory cells and the microenvironment, cytokines and chemokines were also present in the lungs of IKKe^{KA/KA} mice. Increased expression levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1b, IL-6, chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-X-C motif) ligand 5, CCL11 and CCL8 were observed in the lungs of IKKe^{KA/KA} mice as well. Excessive amounts of macrophages also caused increased inflammation, epithelial cell proliferation, DNA damage and activity of many pathways that may contribute to lung carcinogenesis in IKKe^{KA/KA} mice (43,51) (Fig. 2D).

Unlike the malfunction of the nuclear factor κB (NF-κB) pathway in skin cancer (52), increased activity of the canonical NF-κB pathway was found to contribute to lung SCC development in IKKe^{KA/KA} mice. Whether the NF-κB pathway can be used as a therapeutic target to prevent and treat lung SCCs remains to be elucidated (Fig. 2D).

5. The novel role of IKKα in head and neck cancer

IKKα and oral carcinomas. Since IKKα is expressed in normal oral keratinocytes but its expression is frequently decreased in carcinoma cells, further studies have been conducted to investigate the role of IKKα in oral carcinoma tissues and analyze its prognostic significance in comparison with clinicopathological parameters and patient survival. Results indicated that IKKα levels decreased in 44.9% of carcinoma patients and the expression of the protein was closely associated with progression-free survival (PFS), independent of other risk factors. Therefore, IKKα was considered to be a significant independent predictor of mortality due to carcinomas (53).

In vitro, IKKα is located in the nucleus and is upregulated upon differentiation in oral carcinomas. Furthermore, IKKα shows genetic instability in its locus and hypermethylation of its CpG islands (53). Studies have also shown that the genetic instability is frequently associated with promoter hypermethylation, resulting in epigenetic inactivation of gene transcription (54). Otherwise, there is a close correlation between the promoter hypermethylation and microsatellite instability (MSI). MSI, also referred to as simple sequence repeats (SSRs), is originally associated with DNA mismatch repair (MMR), which plays a prominent role in the correction of errors made during DNA replication, genetic recombination and in the repair of small deletions and loops in DNA. Moreover, it closely associates with gene silencing through promoter hypermethylation. Thus, MSI may be important in IKKα-related oral tumorogenesis (55,56). In fact, most of the MSI carcinomas were methylated in a specific site critical for IKKα expression, which is important for the activity of IKKα as a tumor-suppressor gene in oral carcinoma regulation (Fig. 2B). However, since in some carcinomas, the methylation status did not correlate with immunoreactivity, other mechanisms regulating the gene expression remain to be investigated (53,57). Similar to skin cancer, in oral carcinoma, IKKα in the nucleus suppresses malignancy by acting on cell differentiation independent of canonical NF-κB activation in oral carcinoma.

IKKα and nasopharyngeal carcinoma. Nasopharyngeal carcinoma (NPC) is one of the common epithelium-derived carcinomas in the head and neck. The effect of IKKα as the tumor suppressor in NPC cells or the survival of NPC patients has recently been investigated.

IKKα is upregulated upon differentiation in NPC cell lines in vitro. Differential expression of IKKα exists in NPC cells, which is negatively correlated with invasiveness, migration and angiogenesis, but not with proliferation. Lack of IKKα could lead to increased cancer invasion, migration and angiogenesis; on the contrary, reintroduction of IKKα abrogated these biological behaviors (58). Moreover, IKKα inhibited tumorigenesis in mice inoculated with IKKα-transfected NPC cells in vivo. These processes were found to be independent of IKKα kinase activity and the conventional effect of IKKα on NF-κB pathways (58,65).

Furthermore, this study (58) showed that 26.8% of a total of 157 NPC patients exhibited low expression or deletion of IKKα. Although the IKKα expression levels had no correlation with tumor stage, recurrence, distant metastasis, age and gender, the survival (OS or DFS) of NPC patients was significantly associated with IKKα expression. Similar to T stage, lymph node metastasis, locoregional recurrence and distant metastasis, IKKα expression significantly influenced clinical prognosis. Its high expression could serve as an independent favorable predictor for NPC patients.

Similar to oral carcinoma cell lines, the CpG islands of the IKKα gene were heavily methylated in NPC cell lines and clinical specimens. Studies have shown that increased IKKα expression could induce differentiation and prevent NPC development by reducing enhancer of zeste homologue 2 (EZH2)–related H3K27 histone methylation of the IKKα promoter (59). Importantly, overexpression of IKKα results in fusiform morphological change, reduction in CK13 and increase in involucrin and CK8 without activating the NF-κB pathway, leading to differentiation of NPC cells (59-61).
These findings suggest an important role of \(\text{IKK}\alpha\) for NPC differentiation in an epigenetic mechanism. Furthermore, what is the downstream signaling pathway or mechanism that regulates this newly recognized suppressive effect of \(\text{IKK}\alpha\) on NPC? Findings have shown that \(\text{IKK}\alpha\) inhibits NPC development through inactivation of ERK1/2 and its phosphorylation (pERK1/2) in the ERK pathway, but it is independent of EGFR, although it usually acts as the upstream protein in the ERK pathway, thus resulting in aberrant activation of the ERK signaling pathway (65). This finding is consistent with the malfunction of \(\text{IKK}\alpha\) in the proliferation of NPC cell lines (62). Furthermore, matrix metalloproteinase-9 (MMP-9), but not MMP-2, is an essential downstream molecule in the \(\text{IKK}\alpha\)-related ERK pathway for repressing NPC progression (Fig. 2C).

EBV is ubiquitously associated with the carcinogenesis of NPC (63). In addition, research has shown that Epstein-Barr virus EBNA1 inhibits the canonical NF-\(\kappa\)B canonical pathway and contributes to the pathogenesis of NPC, by inhibiting \(\text{IKK}\alpha/\text{IKK}\beta\) phosphorylation (64). Thus, the correlation between \(\text{IKK}\alpha\), EBNA1 and NF-\(\kappa\)B in NPC was investigated, although the expression of EBNA1 was high and undifferentiated expressed in all EBV-positive NPC cell lines. Studies strongly suggest that \(\text{IKK}\alpha\) plays a crucial role as a tumor suppressor in NPC and is not related to tumor-associated protein EBNA1 (65).

6. A different role of \(\text{IKK}\alpha\) in hormone-related breast and prostate cancer

As stated above, \(\text{IKK}\alpha\) plays a pivotal role as a tumor suppressor in epithelial-derived tumors, particularly in SCCs; however, it has been determined that \(\text{IKK}\alpha\) also functions as a tumor promoter in hormone-related breast (66) and prostate cancers (67). One study showed that it provides an important linking effect between RANK signaling and cyclin D1 expression in the development of the mammary gland (68). It was also demonstrated that the C57BL/6 female mouse expresses a mutant \(\text{IKK}\alpha^{AA}\) knock-in allele in which alanine replaces serine to inactivate \(\text{IKK}\alpha\) kinase activity, impairing the proliferation of mammary epithelial cells and thus leading to a severe lactation defect. However, this defect is completely reversed by the reintroduction of a mammary specific cyclin D1 in the \(\text{IKK}\alpha^{AA/AA}\) mammary epithelium. Furthermore, it has been found that \(\text{IKK}\alpha\) kinase activity is involved in cyclin D1 expression and this process is activated by RANK ligand (RANKL), an efficient NF-\(\kappa\)B-x-activator (68).

In breast cancer, \(\text{IKK}\alpha\) phosphorylates ER\(\alpha\) and the nuclear hormone receptor co-activator AIB1/SRC-3 (amplified in breast 1/steroid receptor coactivator-3) and thus activates the transcription of estrogen-responsive genes, including cyclin D1 and c-myc, to enhance proliferation of ER(+) breast cancer cells (66). In addition, another finding showed that the epidermal growth factor receptor (Her-2) activated \(\text{IKK}\alpha\) to induce tumor invasion through the NF-\(\kappa\)B canonical pathway in HER\(\beta^{3/2}\)/ER breast cancer cells (69).

Except for breast cancer, a study demonstrated that nuclear \(\text{IKK}\alpha\) activation by the RANK ligand inhibits maspin expression and leads to metastatic progression of mouse and human prostate cancers (67). Therefore, \(\text{IKK}\alpha\) functions as an oncogenic factor, in conjunction with the hormone-related genes, to contribute to the development of breast and prostate cancers through NF-\(\kappa\)B-dependent or -independent pathways.

7. Conclusions

As a novel and potential suppressor, \(\text{IKK}\alpha\) activates or inactivates comprehensive pathways that prevent the development of a variety of epithelial-derived carcinomas from tumor initiation to progression (Fig. 2). Except for the cytoplasmic effect of \(\text{IKK}\alpha\) on the NF-\(\kappa\)B pathway, the role of nuclear \(\text{IKK}\alpha\) is much more essential to epithelium-derived carcinomas. Although an increasing amount of research has explored the function and mechanism of \(\text{IKK}\alpha\) in such carcinomas, the cross-talk among them has not yet been established. It is still unclear whether \(\text{IKK}\alpha\) deletion targets stage-specific squamous epithelial cells to initiate tumors or it turns on oncogenes or represses tumor suppressors and whether \(\text{IKK}\alpha\) plays a role in stem cell maintenance, renewal or division. On the other hand, \(\text{IKK}\alpha\) is also suggested as a tumor promoter. Therefore, whether \(\text{IKK}\alpha\) functions differently in different types of tumors warrants further investigation. Collectively, \(\text{IKK}\alpha\) is a major regulator to participate in the downstream gene cascade, leading to repression of cell hyperproliferation, angiogenesis, epithelial-mesenchymal transition and malignant progression. Furthermore, \(\text{IKK}\alpha\) may be a potential therapeutic strategy for preventing carcinoma.

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