

TFAP-2: A Special Regulator with Bidirectional Effect in Human Cancer

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Abbreviations: LC: Lung Cancer; TFAP2: Transcription Factor Activator Protein 2; ITPKA: Inositol-trisphosphate 3-kinase A; KRT16: Keratin 16, a type of I cytokeratin; TGFBR1: Transforming Growth Factor Receptor β 1; LCIS: Lobular Carcinoma In situ; MMP9: Matrix Metallprotenaine 9; PTEN: Phosphatase and Tensin homology deleted on chromosome ten; ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; YY1: Yin-Yang1, a transcription factor

Abnormality of transcription factors' activity has been found in signal pathways of many cancers. The AP-2 family of transcription factors (TFAP2) is one of the most representative families with this characteristic. The family, consisting of five members (TFAP2A to TFAP2E), can activate or inhibit the target gene through signal transduction [1]. They have been found to play important roles in human embryonic development [2] and cell differentiation [3]. In addition to their influence on growth and development, TFAP2 family have also been reported to be involved in tumorigenesis and development in cancers of lung, nasopharynx [4], prostate [5], breast [6], glioma [7] and liver [8], etc.

Researches have been focused on the association between TFAP2 family and lung cancer (LC). For example, by inducing ITPKA [9] and KRT16 [10], TFAP2A acts as an oncogene in lung adenocarcinoma and lung tumorigenesis, in coordination with TFAP2C [11]. To further determine the role of TFAP2 in LC, the relationship between this family and the prognosis of LC was explored recently

using bioinformatics in a recent study [12]. There are three significant findings in this study: (1) Compared with normal tissues, the expression of TFAP2A and TFAP2C increase in LC, while the expression of TFAP2B shows no significant difference. (2) Only TFAP2A is associated with the prognosis of LC, whose expression level is negatively correlated with the overall survival rate of LC. (3) The mutation rate of TFAP2A and TFAP2C in LC are higher than that of TFAP2B. Together, these findings suggest TFAP2A has prognostic value, which may improve survival and prognosis accuracy of LC patients.

However, some other researchers have different conclusions about the role of TFAP2B in LC. It is found in one research that the expression of TFAP2B is higher in lung cancer, which suggests poor prognosis [13]. But it is reported in another study that expression of TFAP2B in the nucleus is related to poor survival [14]. One possible reason of these different outcomes is the different sample sizes of the three studies. There were 147 patients contained in Fu's study and totally 241 patients in Kim's study, while Cheng et al. studied 1145 patients. Therefore, selection bias should be taken into consideration. To get further understanding about the role of TFAP2B in lung cancer, clinical studies with larger sample scale are still needed.

In summary, the dysregulation expression level of TFAP2 family and their prognostic value in LC are found in this study. However, except for what have been mentioned in this study, TFAP2 family also have tumor-promoting or inhibiting effect on different cancers.

The Tumor-promoting Effect of TFAP2

The TFAP2 family generally play a promoting role in the progression of cancers such as astrogloma [15], pancreatic cancer [16] and ovarian cancer [17].

In addition to their prognostic value, TFAP2 also show tumor-promoting effect on LC. The upregulation of TFAP2 expression in non-small cell lung cancer is reported in Zhou's study, which is positively related to the pathological stage [18]. As a member of the TFAP2 family, TFAP2C shows similar effect on LC. By mediating the upregulation of TGFBR1 [11], the receptor of transforming growth factor, TFAP2C can enhance the aggressiveness and malignancy of LC. Besides, TFAP2C leads to the oncogenesis of LC through other pathways, including blocking the inhibition of cell cycle, promoting cell-cycle activation [19] and even downregulating the expression of tumor suppressors [20].

It should be noted that TFAP2B is also defined as a tumor promoter. Its overexpression has been associated with alveolar rhabdomyosarcoma [21] and lobular carcinoma *in situ* (LCIS) [22].

The Tumor-inhibiting Effect of TFAP2

The tumor-inhibiting effect of TFAP2 has been widely reported in colorectal cancer and melanoma.

AP-2 α , encoded by TFAP2A, has been related to the suppression of colorectal cancer. It is indicated in Ropponen's study that down-regulation of AP-2 α expression occurs in advanced-grade pathological stages [23]. It is possible that the MMP-9 promoter can be directly bound by AP-2 α [24], resulting in deduced promoter activity. Another explanation is that the expression of PTEN, a tumor suppressor gene, is positively correlated with AP-2 α [25].

Another strong piece of evidence for the inhibitory effect of TFAP2 on cancer comes from studies of melanoma, in which silencing of TFAP2 is related to tumor invasion and metastasis [26]. The loss of TFAP2C expression, influenced by miR-214 [27], can increase microvessel density [26], downregulate the expression of AP-2 α [28] and eventually contribute to the progression of melanoma [29]. Besides, the re-expression of TFAP2C reduces miR-214-induced cell motility and early lung metastasis colonization [28].

In addition, other members of TFAP2 family also have the inhibitory effect on tumor, such as TFAP2B on hepatocellular cancer [30] and TFAP2E on neuroblastoma [31].

The Bidirectional Effect of TFAP2

Interestingly, TFAP2 family sometimes seem to have

bidirectional effect on cancers, among which TFAP2A and TFAP2C are the most representative.

Estrogen receptor(ER) is a useful predictor for breast cancer prognosis [32], which is the basis of endocrine therapy. In one clinical research, it has been found that nuclear AP-2 α encoded by TFAP2A has positive association with ER expression [33], especially in breast cancer with ER-positive [34]. Another research on ER-positive breast tumor-derived cell line also confirms this result [35]. However, the overexpression of HER2, positively related to AP-2 α [36], usually predicts a poor prognosis in breast cancer [37]. It is probably because that AP-2 α can promote HER2 gene transcription [38] in combination with YY1 [39], a cofactor of AP-2 α . And another possible explanation is that the inactivation of AP-2 α protein reduces the activity of HER2 promoter [40].

Encoded by TFAP2C, AP-2 γ seems to play a similar role in breast cancer. In breast tissue, over-expression of the AP-2 γ stimulates cell proliferation and disrupts cell differentiation [41], suggesting that it may have carcinogenic effect. However, it is reported in another research [42] that AP-2 γ can cause blocking of cell cycles by promoting p21 protein, contributing to the suppression of tumor formation. Therefore, TFAP2C may play a dual role [32] in tumor development, initially inhibiting tumor development [42] and then acting in the opposite direction when a certain balance is broken [43]. This conclusion is also confirmed by an *in vivo* experiment [44].

Different effects of TFAP2 family have been showed in Figure 1, which give them broad applications in clinic. For example, the expression of TFAP2A and TFAP2C are elevated in LC compared to normal tissue [12], which may be used as theoretically biomarkers for LC. Furthermore, because of the tumor-promoting effect of TFAP2, they may be considered as a target of anti-tumor drugs. However, there are still some issues to be studied. For instance, in order to detect their expression with the purpose of clinical diagnosis or prognosis, it is necessary to ensure the stable expression level of TFAP2A and TFAP2C in the peripheral circulation. Besides, standardized detection methods are also needed to guarantee sensitivity and specificity of detection [45]. What's more, role of TFAP2B in lung cancer is still controversial. Therefore, we think TFAP2A and TFAP2C could be potential biomarkers and drug targets, but further researches are still needed to solve these problems.

In conclusion, the TFAP2 family play important and complex roles in human cancers. These studies may bring new ideas to the diagnosis, classification, treatment and prognosis of cancer, but there are still many mysteries to be explored. More in-depth studies are required for TFAP2 family to improve targeted therapy and acquire better prognosis.

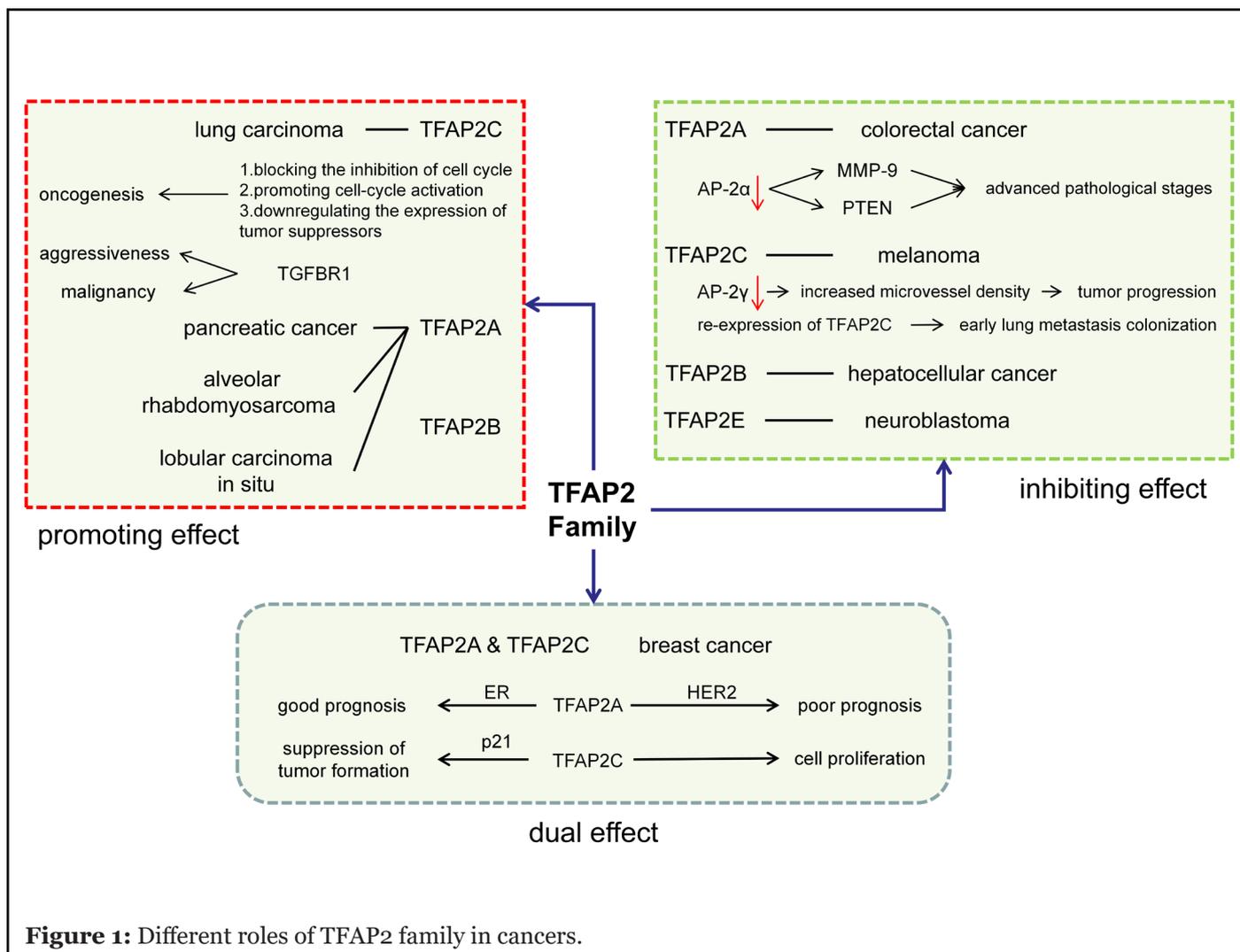


Figure 1: Different roles of TFAP2 family in cancers.

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