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AP-2 Family of Transcription Factors: Critical Regulators of Human Development and Cancer

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ABSTRACT

The AP-2 family of transcription factors consist of DNA-binding proteins: AP-2α to AP-2ε. Members and homologs of this family are also known in frogs, fish and invertebrates. These proteins have the same central basic region and a helix-span-helix dimerization motif, which is necessary for dimerization and DNA binding. This family have been found to influence facial, limbs and kidney development in embryogenesis while regulating differentiation and apoptosis. These proteins are also involved in regulation of endocrine processes. In addition to their influence on growth and development, this family have also been reported to correlate with tumorigenesis and development of cancer. At present, this family have been related to tumors of ovary, melanoma, lung, nasopharynx, breast, glioma, neuroblastoma, colon, etc. They regulate expression of many cancer-related genes and affect the occurrence, development, invasiveness and therapeutic response of cancers. Different expression levels of AP-2s are also related to different survival rate. These findings may bring new idea to the diagnosis, classification, treatment and prognosis of cancer.

The AP-2 transcription factors family (AP-2 family) constitute five DNA-binding proteins: AP-2α to AP-2ε, which are encoded by TFAP2A to TFAP2E, respectively. Frogs, fish and invertebrates also have some members or homologs of this family. Except AP-2δ, the other four of the family are encoded by seven exons and have the same central basic region and a helix-span-helix dimerization motif, which is necessary for dimerization and DNA binding[1]. In addition to its highly similar DNA-binding and dimerization domains with other family members, AP-2δ has unique sequence specificity which has not been observed in other four proteins. This may be useful for regulation of target gene activation[2].

AP-2 family play important roles in regulating cell differentiation and apoptosis. They have been found to influence body development in embryogenesis, including formation of face, limbs, kidney, retina, central nervous system, and heart[3,4]. Mutations or defects of *TFAP2A* and *TFAP2B* lead to developmental malformation[5,6]. These genes are also involved in regulation of endocrine processes. For instance, *TFAP2B* is associated with insulin resistance and diabetes[7], while *TFAP2C* plays a key role in regulating genes of estrogen signaling[8].

In addition to their effect on cell-fate deciding and development, AP-2 family have also been reported to be involved in tumorigenesis and development of cancer. By far, this family have been found to be closely associated with various tumors, including ovarian cancer,

melanoma, lung cancer, nasopharygeal cancer, breast cancer, glioma, neuroblastoma, gastric cancer, colon cancer, ect.[9-17]. They regulate the expression of many cancer-related genes, especially in breast cancer. Moreover, they coordinate with the occurrence, development, invasiveness and therapeutic response of cancers. Different expression levels of AP-2s are also related to different survival rate.

AP-2α

AP-2α encoded by *TFAP2A* regulates cell growth and tissue differentiation. Its expression has been observed in epithelial and neural crest cell lineages in early stage of murine embryogenesis[3]. Mutations of *TFAP2A* have been found to result in Branchio-oculo-facial syndrome (BOFS), a rare orofacial cleft syndrome which includes cutaneous, ocular, renal and ectodermal anomalies, along with characteristic facial appearance[5].

Different expression levels of AP-2α have also been reported in cancer cells.

Overexpression of AP-2α has been found in tumors of ovary, nasopharynx and lung, and the increased expression may promote tumorigenesis and lead to deteriorate outcome for cancers. In epithelial cells of normal ovary, AP-2α protein is only expressed in the cytoplasm. But in malignant epithelial ovarian tumors, AP-2α is expressed both in the nucleus and cytoplasm. The expression level of AP-2α in the nucleus is related to increased risk of dying[9]. High expression of AP-2α has also been reported in nasopharyngeal carcinoma cells, which promotes tumor growth, whereas the downregulation of AP-2α expression inhibits cell viability and suppresses tumor growth along with microvessel density[14]. The up-regulated expression level is also found in lung carcinoma, which is highly associated with poor prognosis[12]. This outcome is consistent with another study, in which *TFAP2A* upregulates the expression of *KRT16*, an independent prognosis predictor related to bad survival for lung cancer[18].

In some other cancers, however, the expression of AP-2α is decreased, which is related to tumor progression. For example, suppressed expression of AP-2α in breast cancer seems to occur more frequently in invasive breast tumors than in ductal carcinoma in situ[19]. Similarly, AP-2α expression correlates inversely with glioma grade, which may suggest its direct role in glioma tumorigenicity[11]. The association between reduced AP-2α expression and increased tumorigenicity is also observed in colon cancer cells[17] and gastric adenocarcinoma[20].

AP-2β

AP-2β plays a critical role in development of ductus arteriosus and limb patterning[21]. *TFAP2B* mutation leads to nonsyndromic patent ductus arteriosus and Char syndrome, which is characterized by patent ductus arteriosus, facial dysmorphism and abnormalities of the fifth finger[6,22]. Besides, AP-2β is also involved in glucose and fat metabolism. Gene variations of *TFAP2B* are related to insulin resistance and type 2 diabetes mellitus[7]. It has also been reported to influence adiposity-related conditions and intrauterine growth[23].

Similar to AP-2α, reduced or increased *TFAP2B* expression has also been reported in human cancers. Enhanced expression of AP-2β has been reported in lobular carcinoma in situ(LCIS) and invasive lobular breast cancer[24]. In addition, overexpression of AP-2β is related to poor prognosis in lung adenocarcinoma[25] and papillary thyroid cancer[26], while decreased expression seems to be correlated with unfavorable prognosis and adverse patient outcome in neuroblastoma[15] and endometrial carcinoma[27].

AP-2γ

Studies have suggested the relationship between AP-2γ and lung carcinoma. AP-2γ acts as an oncogenic factor promoting lung tumorigenesis[28] and has a critical role in lung cancer development[29]. Besides, in lung carcinoma cells, the expression of AP-2γ is detected to be increased[12], which inhibits the expression of *GADD45B* and *PMAIP1*, then promotes proliferation and motility of cells in non-small cell lung cancer[30].

Interestingly, AP-2γ has been reported to have opposite effects on breast cancer: it firstly delayed tumor initiation, however then promoted tumor progression[13]. *TFAP2C* has been found to influence development of the luminal cell type during mammary development and to act as a critical transcriptional regulator, which maintains the luminal phenotype[31]. *TFAP2C* regulates expression of many genes in breast cancer. *TFAP2C* is firstly reported to induce high expression of *ERBB2(Her2)* and *ESR1 (ERa)*, which influences hormone response in breast cancer cells[8]. Furthermore, studies have suggested *TFAP2C* coordinates the expression of some other primary target genes, including *FOXA1, WWOX, GREB1, CDH2, HPSE, IGSF11*, etc[32,33]. The expression level of *TFAP2C* also coordinates with treatment response and survival rate of patients with breast cancer. High expression of *TFAP2C* has been reported to repress *CD44*, a basal-associated gene of breast cancer, and lead to a higher rate of pathologic complete response after neoadjuvant chemotherapy[34]. However, another research suggests that overexpression of *TFAP2C* is associated with a shorter survival beyond 10 years of diagnosis[35].

AP-2δ

Researches on AP-2δ and *TFAP2D* are relatively rare. Compared with other members of AP-2 family, AP-2δ seems to influence mammalian development in a different way. Expression of AP-2δ has been reported in retina, the central nervous system, and the developing heart, while

the neural crest, facial mesenchyme, and limbs hardly shows any expression[4]. Expression of AP-2δ in ganglion cells promotes the fine-tuning of axonal growth in the developing retina[36]. Besides, loss of AP-2δ coordinates with reduced axonal projections to the superior colliculus[37].

AP-2δ has also been found in tissue of the prostate[38]. Moreover, in aggressive tumor phenotype of prostate cancer, upregulation of AP-2δ is detected[39].

AP-2ε

Many studies of AP-2ε concentrate on its prediction value on patients' response to chemotherapy and outcome in colorectal cancer. However, this issue is still under dispute. Elbert's study indicates that hypermethylation of *TFAP2E* is correlated with resistance to chemotherapy in colorectal cancer[40], while another research shows the response to chemotherapy cannot be predicted by the level of methylation[41]. As for the value of predicting prognosis, there's also no consensus. Some studies show hypermethylation is associated with survival advantage[42] while the correlation with poorer overall and disease-free survival has also been reported[43].

In addition, AP-2ε is also associated with human neuroblastoma. It is reported that AP-2ε is involved in the regulation of DNA damage response in neuroblastoma cells[44].

The AP-2 family of transcription factors play irreplaceable roles in embryogenesis, body formation and development. *TFAP2A* and *TFAP2B* are also involved in regulation of endocrine processes. In addition, the family have also been found to be involved in tumorigenesis, development and prognosis of a variety of human cancers. And now they are still being studied extensively in human cancer. Considering the influence of AP-2 family on tumor type, therapeutic response and prognosis, especially as demonstrated in breast and colorectal cancers, these studies may bring new idea to the diagnosis, classification, treatment and prognosis of cancer. Meanwhile, there are still many controversial issues, including AP-2ε's prediction value on patients' response to chemotherapy and outcome in colorectal cancer, to be studied.

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Abbreviations

TFAP: transcription factor activating proteins.

KRT16: gene of keratin 16, a type of I cytokeratin

GADD45B: gene of growth arrest and DNA-damage-inducible beta

PMAIP1: gene of phorbol-12-myristate-13-acetate-induced protein 1

ERBB2: V-Erb-B2 Avian Erythroblastic Leukemia Viral Oncogene Homolog 2

Her2: gene of human epidermal growth factor receptor-2

ESR1: gene of estrogen receptor 1

ERa: gene of estrogen receptor α

FOXA1: gene of forkhead box protein A1

WWOX: gene of WW domain-containing oxidoreductase

GREB1: gene of growth regulation by estrogen in breast cancer 1

CDH2: gene of N-cadherin

HPSE: gene of heparanase

IGSF11: gene of immunoglobulin superfamily member 11

CD44: gene of cluster of differentiation 44

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