Transcription factor AP-2beta in development, differentiation and tumorigenesis

Mieke Raap | Lisa Gierendt | Hans H. Kreipe | Matthias Christgen

Institute of Pathology, Hannover Medical School, Hannover, Germany

Correspondence
Mieke Raap, Institute of Pathology, Hannover Medical School, Carl-Neuberg Street 1, 30625 Hannover, Germany.
Email: raap.mieke@mh-hannover.de

Abstract
To date, the AP-2 family of transcription factors comprises five members. Transcription factor AP-2beta (TFAP2B/AP-2β) was first described in 1995. Several studies indicate a critical role of AP-2β in the development of tissues and organs of ectodermal, neuroectodermal and also mesodermal origin. Germline mutation of TFAP2B is known to cause the Char syndrome, an autosomal dominant disorder characterized by facial dysmorphism, patent ductus arteriosus and anatomical abnormalities of the fifth digit. Furthermore, single-nucleotide polymorphisms in TFAP2B were linked to obesity and specific personality traits. In neoplasias, AP-2β was first described in alveolar rhabdomyosarcoma. Immunohistochemical staining of AP-2β is a recommended ancillary test for the histopathological diagnosis of this uncommon childhood malignancy. In neuroblastoma, AP-2β supports noradrenergic differentiation. Recently, the function of AP-2β in breast cancer (BC) has gained interest. AP-2β is associated with the lobular BC subtype. Moreover, AP-2β controls BC cell proliferation and has a prognostic impact in patients with BC. This review provides a comprehensive overview of the current knowledge about AP-2β and its function in organ development, differentiation and tumorigenesis.

KEYWORDS
breast cancer, Char syndrome, kidney, neuroblastoma, obesity

1 | THE AP-2 FAMILY OF TRANSCRIPTION FACTORS

The transcription factor AP-2 protein was first purified from HeLa cells in 1987.1 Subsequently, a spatially restricted expression pattern of AP-2 in the neural crest, the nervous system and surface epithelium was described.2 In 1995, Moser et al cloned and characterized a second member of the AP-2-family of transcription factors, which was designated as transcription factor AP-2β.3 To date, five members of this transcription factor family are described, namely AP-2α, AP-2β, AP-2γ, AP-2δ and AP-2ε, which are encoded by separate genes (TFAP2A, TFAP2B, TFAP2C, TFAP2D, TFAP2E).4 Although expression of AP-2ε seems to be restricted to the central nervous system,5 AP-2α, AP-2β and AP-2γ show partially overlapping expression patterns in the facial mesenchyme, the limbs and various epithelia.6,7,8 (Figure 1). Despite their similar expression patterns AP-2α, AP-2β and AP-2γ have not only redundant but also nonredundant roles during embryogenesis, differentiation and cellular homeostasis.9,10 Data regarding AP-2α need to be interpreted with caution. Most results were obtained before 1995, when only nonspecific antibodies binding to multiple AP-2-family members were available. In conventional

Abbreviations: BC, breast cancer; ccRCC, clear cell renal cell cancer; DBH, dopamine β-hydroxylase; RA, retinoic acid; SNPs, single-nucleotide polymorphisms.
mouse knockout studies, loss of AP-2α resulted in failure of cranial closure and dismorphogenesis of the facial skeleton and the limbs.12-14 This is in line with the conclusion of Milunsky et al that TFAP2A mutations are causative for the branchiooculofacial syndrome in humans.15

Knockout mice lacking AP-2γ die soon after implantation because of the dysfunctional proliferation and differentiation of extraembryonic trophoectodermal cells.16-18 However, knockout mice lacking AP-2β die postnatally because of renal failure induced by increased apoptosis of epithelial cells in the collecting duct and distal tubules and norepinephrine deficiency.19-22 In cancer, AP-2α and AP-2γ have been in the focus of research for many years. As reviewed by Kolat et al, AP-2α and AP-2γ have different functions in carcinogenesis.23 For example, in breast cancer (BC), hepatocellular cancer, melanoma, glioblastoma, gastric cancer and prostate cancer AP-2α-expression is associated with less aggressive tumors or a better clinical outcome by regulation of apoptosis, tumor cell growth, differentiation and chemotherapy sensitivity.23 On the other hand, in neuroblastoma, acute myeloid leukemia and squamous cell carcinoma AP-2α was shown to promote tumor cell growth and aggressiveness.23 AP-2γ seems to have mostly onco-genic functions. Expression of AP-2γ is associated with a more aggressive tumor behavior in BC, melanoma, neuroblastoma, ovarian and testicular cancer, while its function in lung cancer remains controversial.23

For almost 20 years, AP-2α and AP-2γ have been in the focus of biomedical research, but recently the function of AP-2β in nonneoplastic and neoplastic conditions has gained interest. This review summarizes the current knowledge about the transcription factor AP-2β.

2 | TFAP2B GENE AND AP-2β-PROTEIN STRUCTURE

The transcription factor AP-2beta (TFAP2B) gene is located on chromosome 6p12. It is composed of 7 exons of 32.5 kb.24 Isotype-specific sequence conservation is retained across many species, especially in human, mouse and chicken.11,25 Two polymorphic regions have been described. One is located in the second intron between nucleotides 12593 and 12612, close to the 3' splice site of Exon 2. It consists of four or five CAAA repeats. The other polymorphic region is a single-nucleotide polymorphism (SNP), that is, G/A substitution, located at −67 bp upstream of exon 1.19

AP-2 proteins form hetero- and homodimers.3,26 The AP-2 transcription factors share a unique C-terminal helix-span-helix homodimerisation motif, which begins with a glutamine amino acid adjacent to a basic region. The DNA-binding domains are located in these regions. Therefore, all AP-2 transcription factors bind to similar DNA-target regions, preferentially to the palindromic consensus sequence 5'-GCCN3GGC-3' and other G/C-rich elements with variable

![FIGURE 1](image-url) Expression of transcription factor AP-2 family members in normal nonneoplastic tissues of human adults. Data shown are a summary of expression profiling by high-throughput sequencing modified according to (A) BioProject: PRJEB4337 and (B) BioProject: PRJEB2445. X-axis displays tissues analyzed for TFAP2A, -B, -C and -E. TFAP2D is not included because its expression is limited to the central nervous system. Y-axis displays reads per kilobase per million mapped reads (RPKM). C, Examples of immunohistochemical stains of AP-2β in adult human tissues.10
affinities. Several candidate target genes have been described. These include genes that are involved in important biological processes, such as CDKN2A, ErbB2 or MYC. The AP-2 amino acid sequences are relatively less conserved at their proline- and glutamine-rich N-terminals, where the activation domains are located. Hence, nonredundant functions of AP-2 transcription factors may possibly be explained by different activation mechanisms.

3 | AP-2β IN EMBRYOGENESIS, DEVELOPMENT AND CELLULAR DIFFERENTIATION

AP-2β shows a nearly identical expression pattern in mouse and human embryonic and adult tissues. This was demonstrated by comparison of immunohistochemical stains and in situ hybridization of human vs mouse embryonic tissues and human vs mouse adult tissues, using whole mount and microarray techniques. AP-2β plays a critical role in the development of several tissues and organs of ectodermal, neuroectodermal and also mesodermal origins (Table 1).

Moser et al showed that AP-2β is essential for late-stage development of the collecting ducts and distal tubules of the kidney. Knockout of AP-2β in mice induced apoptosis of tubular epithelium, possibly due to activation of c-myc. This led to kidney cyst formation and early postnatal death. Also in the human adult kidney, AP-2β can be detected in the distal tubules (Figure 1).

Germine mutations of TFAP2B cause the Char syndrome, an autosomal dominant disorder characterized by facial dysmorphism, patent ductus arteriosus and anatomical abnormalities of the fifth digit. Facial dysmorphisms and patent ductus arteriosus might be explained by data from nonmammalian model organisms. Studies on sea lamprey and avian models indicate that AP-2β is involved in neural crest cell specification and migration, which is of importance for facial morphogenesis and branchial arch patterning.

Studies on human and mouse embryonic tissue show an expression of AP-2β in the facial mesenchyme. The periocular mesenchyme gives rise to several structures of the eye, such as the corneal stroma and endothelium, ciliary body stroma and muscle, anterior iris stroma and drainage structures. TFAP2B knockout in murine neural crest cells by Wnt1-Cre knockout resulted in significantly reduced levels of norepinephrine and epinephrine, which might be a further cause of the early postnatal death of AP-2β−/− mice.

Further studies suggesting a role of AP-2β in monoaminergic synthesis regulation have been published by Damberg et al. Ho in the polymorphic second intron seems to be associated with anxiety-related personality traits in women, but interestingly not in men, accompanied by a decreased level of monoamine oxidase. Moreover, the polymorphism seems to be associated with eating disorders such as binge-eating. This is of interest as in genome-wide association studies SNPs in the second intron of TFAP2B have also been linked to Type 2 diabetes mellitus and SNPs in the third intron to obesity. Central deregulation of eating behavior might be an explanation for these findings. Other authors favor a direct influence on metabolism as explanation for the observed associations. Approaches using the murine adipocyte cell line 3T3-L1 demonstrated an increase in lipid accumulation, glucose uptake, impaired insulin signaling and decreased secretion of leptin and adiponectin due to AP-2β overexpression.

A variety of other human tissues and organs express AP-2β. However, AP-2β function has not yet been studied in these cellular contexts (Table 1). For example, AP-2β is expressed in the basal epithelial cell layer of the squamous epithelium of the esophagus and in a subset of basal epithelial cells in the oral mucosa, suggesting a role for AP-2β in the stem cell compartment in these tissues. Furthermore, AP-2β is expressed in apocrine sweat glands of the skin and in a subset of epithelial cells in salivary glands. In the normal mammary gland, AP-2β shows a scattered expression pattern in the luminal cell compartment and is strongly expressed in apocrine metaplasia and usual ductal hyperplasia. Other members of the AP-2 family, namely AP-2α and AP-2γ, were shown to be expressed in a particular spatiotemporal manner, suggesting a role for initiation or coordination of budding and branching of the fetal breast anlage. A closely related function of AP-2β is conceivable and is currently being investigated by our group.

In summary, AP-2β is involved in the development and differentiation of very different tissues of ectodermal, neuroectodermal and also mesodermal origin including kidney, facial mesenchyme, central and peripheral nervous system and the mammary gland. So far, our knowledge about the function of AP-2β is mainly based on embryonic studies. Only few studies have addressed the function of AP-2β in postnatal adult tissues.

4 | AP-2β IN MALIGNANT NEOPLASIAS

One of the first malignant neoplasias, in which AP-2β was described and analyzed, is the alveolar rhabdomyosarcoma (aRMS). aRMS is an uncommon childhood malignancy. Approximately 80% of aRMSs
**TABLE 1** Expression and function of AP-2β in normal embryonic and adult tissues and neoplasms

| Tissue | Function/expression of AP-2β | References |
|--------|------------------------------|------------|
| **Embryonic tissues** | | |
| Kidney | • Development of collecting duct and distal tubules | 19, 20 |
| Facial mesenchyme | • Germline mutation of TFAP2B causes Char syndrome | 31–35 |
| | • Development of the anterior eye segment | 7, 36 |
| Central nervous system (roof of midbrain, hindbrain) | Association of genetic variances of TFAP2B with | 37, 38 |
| | • Diabetes mellitus type 2 | 39–45 |
| | • Obesity | 46–49 |
| | • Specific personality traits | |
| Peripheral nervous system/adrenal medulla | • Differentiation of norepinephrine producing sympathetic neurons | 21, 22 |
| **Adult tissues** | | |
| Adrenal medulla | • Regulation of catecholamine biosynthesizing enzymes | 21, 22, 50 |
| Mammary gland | • Protein/RNA expression in scattered luminal epithelial cells | 10 |
| | • Protein expression in apocrine metaplasia and usual ductal hyperplasia | |
| Others | • Function unknown | |
| | Protein expression | 10 |
| | • In distal tubuli of the kidney | |
| | • In the basal epithelial cell layer of the esophagus | |
| | • In apocrine sweat glands | |
| | • In keratinocytes of the skin | |
| | • In a subset of epithelial cells of salivary glands | |
| | • Function unknown | |
| **Neoplasias** | | |
| Alveolar rhabdomyosarcoma | • Antiapoptotic signal of AP-2β as downstream effector of PAX3-FOX01 fusion protein | 51–54 |
| Breast cancer | • Association with lobular breast cancer subtype | 10, 55 |
| | • Favorable prognostic factor | |
| | • Control of tumor cell proliferation | |
| | • Induction of luminal differentiation by interference with RSPO1 and induction of SPDEF | |
| Neuroblastoma | • Noradrenergic differentiation | 56, 57 |
| | • Crucial for retinoic acid induced differentiation | |
| Renal cell cancer | • Favorable prognostic factor | 58, 59 |
| Lung cancer | • Control of cancer cell growth by activation of hTERT in lung cancer cell lines | 60, 61 |
| | • No relevant protein expression in tissue based human lung cancer studies | 62 |
| Endometrial cancer | • Favorable prognostic factor | 63 |
| Cervical cancer | • Favorable prognostic factor | 60, 61, 64 |

*Note: Tabular overview of the current knowledge about the functions of AP-2β in the development, differentiation and neoplastic transformation of different tissues.*
harbor translocations t(2;13) or t(1;13), which juxtapose the PAX3 or PAX7 gene with FOXO1. The PAX3-FOXO1 fusion protein induces TFAP2B, which is its direct downstream effector and drives aRMS growth by antiapoptotic signals. Fluorescence in situ hybridization for FOXO1 rearrangement and/or immunohistochemical detection of AP-2β with the H-87 antibody are recommended ancillary tests for the histopathological diagnosis of aRMS. The FOXO1 rearrangement is an unfavorable prognostic factor and expression of AP-2β has the same prognostic implication.

The analysis of AP-2β in malignant neoplasias has recently gained wider interest (Table 1). Interestingly, contrary to the results in aRMS, AP-2β seems to be a favorable prognostic marker in carcinomas such as endometrial cancer, cervical cancer, renal cell cancer and BC. Likewise, in neuroblastoma, AP-2β was shown to be a marker of tumor differentiation and favorable outcome.

Neuroblastoma is one of the most common malignancies in children. Neuroblastoma is derived from embryonal precursor cells of the sympathetic nervous system. As in normal sympathoadrenal cells, AP-2 is important for noradrenergic differentiation in this neoplasm. In neuroblastoma cell lines, AP-2β induces an upregulation of the enzymes DBH and tyrosine hydroxylase, which are involved in catecholamine biosynthesis. Retinoic acid (RA) is a drug used for antitumoral therapy in neuroblastoma patients. AP-2β is required for RA-induced differentiation of neuroblastoma cell lines. Therefore, AP-2β might serve as a marker for RA therapy responsiveness. CpG methylation of the TFAP2B locus was shown to be the major cause of changes in AP-2β expression levels in neuroblastoma and not copy number alterations or mutations.

AP-2β is important for kidney development, but data regarding AP-2β in renal cancer are relatively sparse. In clear cell renal cell cancer (ccRCC), AP-2β expression is considerably decreased in comparison with normal renal tubules. This might be due to a loss of AP-2β expression during carcinogenesis. As AP-2β is only expressed in distal but not proximal tubule epithelium of the adult kidney, an alternative explanation might be the often postulated origin of ccRCC from proximal renal epithelial progenitor cells. In lung cancer cell lines, AP-2β controls tumor cell growth by activation of hTERT. However, in tissue-based studies of human lung cancer, no relevant expression of AP-2β was found.

In BC, the expression of AP-2β has also gained interest. Two well-designed studies of microarray gene expression data have shown an association of AP-2β with the lobular BC subtype. This association was validated by detailed immunohistochemical analyses of large BC patient cohorts. Moreover, AP-2β is associated with favorable clinicopathological prognostic factors such as ER expression and low Ki67 and with a favorable clinical outcome. In vitro data indicate that AP-2β controls tumor cell proliferation in lobular BC cell lines. In BCs from various genetically engineered mouse (GEM) models, AP-2β is not expressed although normal murine breast epithelium shows a scattered expression pattern like in the human mammary gland. Yoldi et al described downregulation of AP-2β by RANK activation in hormone-receptor negative MMTV-PyMT murine BC. Furthermore, they showed that AP-2β induces luminal differentiation in BC by interfering with the induction of Wnt agonist RSPO1 and by inducing SPDEF. Differential methylation of TFAP2B in normal breast tissue is associated with a higher risk of developing BC.

In summary, AP-2β regulates differentiation and proliferation in various nonneoplastic and neoplastic conditions. The understanding of AP-2β associated signaling pathways is still evolving. Further studies on AP-2β are warranted and will increase the understanding of its functions and complex roles in development, differentiation and tumorigenesis.

ACKNOWLEDGMENT
Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

ORCID
Mieke Raap https://orcid.org/0000-0001-8338-6209

REFERENCES
1. Mitchell PJ, Wang C, Tjian R. Positive and negative regulation of transcription in vitro: enhancer-binding protein AP-2 is inhibited by SV40 T antigen. Cell. 1987;50(6):847-861.
2. Mitchell PJ, Timmons PM, Hebert JM, Rigby PW, Tjian R. Transcription factor AP-2 is expressed in neural crest cell lineages during mouse embryogenesis. Genes Dev. 1991;5(1):105-119.
3. Moser M, Imhof A, Pscherer A, et al. Cloning and characterization of a second AP-2 transcription factor: AP-2 beta. Development. 1995;121(9):2779-2788.
4. Pellikkainen JM, Kosma VM. Activator protein-2 in carcinogenesis with a special reference to breast cancer—a mini review. Int J Cancer. 2007;120(10):2061-2067.
5. Hesse K, Vaupel K, Kurt S, Buettnner R, Kiefer J, Moser M. AP-2delta is a crucial transcriptional regulator of the posterior midbrain. PLoS One. 2011;6(8):e23483.
6. Moser M, Ruschhoff J, Buettnner R. Comparative analysis of AP-2 alpha and AP-2 beta gene expression during murine embryogenesis. Dev Dyn. 1997;208(1):115-124.
7. Martino VB, Sabljic T, Deschamps P, et al. Conditional deletion of AP-2beta in mouse cranial neural crest results in anterior segment dysgenesis and early-onset glaucoma. Dev Mol Mech. 2016;9(8):849-861.
8. Seki R, Kitajima K, Matsubara H, et al. AP-2beta is a transcriptional regulator for determination of digit length in tetrapods. Dev Biol. 2015;407(1):75-89.
9. Fagerberg L, Hallstrom BM, Oksvold P, et al. Analysis of the human proteome by parallel tag identification. Nature. 2013;503(7471):75-81.
10. Schorle H, Meier P, Buchert M, Jaenisch R, Mitchell PJ. Transcription factor AP-2 essential for cranial closure and craniofacial development. Nature. 1996;381(6579):238-241.
14. Nottoli T, Hagopian-Donaldson S, Zhang J, Perkins A, Williams T. AP-2-null cells disrupt morphogenesis of the eye, face, and limbs in chimeric mice. Proc Natl Acad Sci USA. 1998;95(23):13714-13719.

15. Milunsky JM, Maher TA, Zhao G, et al. TFAP2A mutations result in branchio-oculo-facial syndrome. Am J Hum Genet. 2008;82(5):1171-1177.

16. Auman HJ, Nottoli T, Lakiza O, Winger Q, Donaldson S, Williams T. Transcription factor AP-2gamma is essential in the extra-embryonic lineages for early postimplantation development. Development. 2002;129(11):2733-2747.

17. Werling U, Schorle H. Transcription factor gene AP-2 beta is essential for early murine development. Mol Cell Biol. 2002;22(9):3149-3156.

18. Cao Z, Carey TS, Ganguly A, Wilson CA, Paul S, Knott JG. Transcription factor AP-2gamma induces early Cdx2 expression and represses HIPPO signaling to specify the trophectoderm lineage. Development. 2015;142(9):1606-1615.

19. Moser M, Pscherer A, Roth C, et al. Enhanced apoptotic cell death of renal epithelial cells in mice lacking transcription factor AP-2beta. Genes Dev. 1997;11(15):1938-1948.

20. Moser M, Dahmen S, Kluge R, et al. Terminal renal failure in mice lacking transcription factor AP-2 beta. Lab Invest. 2003;83(4):571-578.

21. Hong SJ, Lardaro T, Oh MS, et al. Regulation of the noradrenaline neurotransmitter phenotype by the transcription factor AP-2beta. J Biol Chem. 2008;283(24):16860-16867.

22. Hong SJ, Huh YH, Leung A, et al. Transcription factor AP-2beta regulates the neurotransmitter phenotype and maturation of chromaffin cells. Mol Cell Neurosci. 2011;44(1):245-251.

23. Kost D, Kaluznińska Z, Bednarek AK, Plucienik E. The biological characteristics of transcription factors AP-2α and AP-2γ and their importance in various types of cancers. Bioclı. Rep. 2019;39(3):BSR20181928. https://doi.org/10.1042/BSR20181928 Print 2019 Mar 29.

24. Williamson JA, Bosher JM, Skinner A, Sheer D, Williams T, Hurst HC. Chromosomal mapping of the human and mouse homologues of two new members of the AP-2 family of transcription factors. Genomics. 1996;35(1):262-264.

25. Wankhade S, Yu Y, Weinberg J, Tainsky MA, Kannan P. Characterization of the activation domains of AP-2 family transcription factors. J Biol Chem. 2000;275(38):29701-29708.

26. Williams T, Tjian R. Characterization of a dimerization motif in AP-2 and its function in heterologous DNA-binding proteins. Science. 1991;251(4997):1067-1071.

27. Mohibullah N, Donner A, Ippolito JA, Williams T. SELEX and missing protein: DNA binding complex. Nucleic Acids Res. 1999;27(13):2760-2769.

28. Zeng YX, Somasundaram K, el-Deiry WS. AP2 inhibits cancer cell growth and activates p21WAF1/CIP1 expression. Nat Genet. 1997;15(1):78-82.

29. Bosher JM, Williams T, Hurst HC. The developmentally regulated transcription factor AP-2 is involved in c-erbB-2 overexpression in human mammary carcinoma. Proc Natl Acad Sci USA. 1995;92(3):744-747.

30. Gauthier S, Imhof A, Dosch R, et al. Transcriptional activation by Myc is under negative control by the transcription factor AP-2. EMBO J. 1995;14(7):1508-1519.

31. Satoda M, Zhao F, Diaz GA, et al. Mutations in TFAP2B cause Char syndrome, a familial form of patent ductus arteriosus. Nat Genet. 2000;25(1):42-46.

32. Hockman D, Chong-Morrison V, Green SA, et al. A genome-wide assessment of the ancestral neural crest gene regulatory network. Nat Commun. 2019;10(1):4698-019-12687-4.

33. Ling ITC, Sauka-Spengler T. Early chromatin shaping predetermines multipotent vaginal neural crest into neuronal, neuronal and mesenchymal lineages. Nat Cell Biol. 2019;21(12):1504-1517.

34. Van Otterloo E, Li H, Jones KL, Williams T. AP-2alpha and AP-2beta cooperatively orchestrate homeobox gene expression during branchial arch patterning. Development. 2018;145(2):1-15. https://doi.org/10.1242/dev.157438.

35. Timberlake AT, Jin SC, Nelson-Williams C, et al. Mutations in TFAP2B and previously unimplicated genes of the BMP, Wnt, and hedgehog pathways in syndromic craniosynostosis. Proc Natl Acad Sci USA. 2019;116(30):15116-15121.

36. Akula M, Taiyab A, Deschamps P, et al. AP-2γ is required for formation of the murine trabecular meshwork and Schlemm’s canal. Exp Eye Res. 2020;195:108042.

37. Maeda S, Tsukada S, Kanazawa A, et al. Genetic variations in the gene encoding TFAP2B are associated with type 2 diabetes mellitus. J Hum Genet. 2005;50(6):283-292.

38. Liu Q, Pan J, Berzuci N, Rutter MK, Guo H. Integrative analysis of Mendelian randomization and Bayesian colocalization highlights four genes with putative BMI-mediated causal pathways to diabetes. Sci Rep. 2020;10(1):7476-020-64493-4.

39. Lindgren CM, Heid IM, Randall JC, et al. Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. PLoS Genet. 2009;5(6):e1000508.

40. Graff M, North KE, Richardson AS, et al. BMI loci and longitudinal BMI from adolescence to young adulthood in an ethnically diverse cohort. Int J Obes (Lond). 2017;41(5):759-768.

41. Joost U, Villa I, Comasco O, Oreland L, Veidebaum T, Harro J. Association between transcription factor AP-2β genotype, obesity, insulin resistance and dietary intake in a longitudinal birth cohort study. Int J Obes (Lond). 2019;43(10):2095-2106.

42. Tao Y, Maegawa H, Ugi S, et al. The transcription factor AP-2beta causes cell enlargement and insulin resistance in 3T3-L1 adipocytes. Endocrinology. 2006;147(4):1685-1696.

43. Meng X, Kondo M, Morino K, et al. Transcription factor AP-2beta: a negative regulator of IRS-1 gene expression. Biochem Biophys Res Commun. 2010;392(4):526-532.

44. Fukuda K, Yoshizaki T, Kondo M, et al. Transcription factor AP-2beta inhibits expression and secretion of leptin, an insulin-sensitizing hormone, in 3T3-L1 adipocytes. Endocrinology. 2001;142(7):2201-2208.

45. Ikeda K, Maegawa H, Ugi S, et al. Transcription factor activating enhancer-binding protein-2beta. A negative regulator of adiponectin gene expression. J Biol Chem. 2006;281(42):31245-31253.

46. Damberg M, Garpenstrand H, Hallman J, Oreland L. Genetic mechanisms of behavior—don’t forget about the transcription factors. Mol Psychiatry. 2001;6(5):503-510.

47. Gamero-Villarreal C, Gonzalez LM, Rodriguez-Lopez R, et al. Influence of TFAP2B and KCTD15 genetic variability on personality dimensions in anorexia and bulimia nervosa. Brain Behav. 2017;7(9):e00784.

48. Damberg M, Berggard C, Mattila-Evenden M, et al. Transcription factor AP-2beta genotype associated with anxiety-related personality traits in women. A replication study. Neuropsychobiology. 2003;48(4):169-175.

49. Damberg M, Garpenstrand H, Berggard C, Asberg M, Hallman J, Oreland L. The genotype of human transcription factor AP-2beta is associated with platelet monoamine oxidase B activity. Neurosci Lett. 2000;291(3):204-206.

50. Damberg M. Transcription factor AP-2 and monoaminergic functions in the central nervous system. J Neural Transm (Vienna). 2005;112(10):1281-1296.

51. Wachtel M, Runge T, Leuschner I, et al. Subtype and prognostic classification of rhombomoyaosoma by immunohistochemistry. J Clin Oncol. 2006;24(5):816-822.

52. Ebauer M, Wachtel M, Niggl F, Schafer BW. Comparative expression profiling identifies an in vivo target gene signature with TFAP2B as a mediator of the survival function of PAX3/FKHR. Oncogene. 2007;26(51):7267-7281.

53. Grass B, Wachtel M, Behnke S, Leuschner I, Niggl F, Schafer BW. Immunohistochemical detection of EGFR, fibrillin-2, P-cadherin and...
AP2beta as biomarkers for rhabdomyosarcoma diagnostics. *Histopathology*. 2009;54(7):873-879.

54. Rudzinski ER, Anderson JR, Lyden ER, et al. Myogenin, AP2beta, NOS-1, and HMGA2 are surrogate markers of fusion status in rhabdomyosarcoma: a report from the soft tissue sarcoma committee of the children's oncology group. *Am J Surg Pathol*. 2014;38(5):654-659.

55. Yoldi G, Pellegrini P, Trinidad EM, et al. RANK signaling blockade reduces breast cancer recurrence by inducing tumor cell differentiation. *Cancer Res*. 2016;76(19):5857-5869.

56. Ikram F, Ackermann S, Kahlert Y, et al. Transcription factor activating protein 2 beta (TFAP2B) mediates noradrenergic neuronal differentiation in neuroblastoma. *Mol Oncol*. 2016;10(2):344-359.

57. Thorell K, Bergman A, Caren H, et al. Verification of genes differentially expressed in neuroblastoma tumours: a study of potential tumour suppressor genes. *BMC Med Genomics*. 2009;2:53.

58. Oya M, Mikami S, Mizuno R, et al. Differential expression of activator protein-2 isoforms in renal cell carcinoma. *Urology*. 2004;64(1):162-167.

59. Tun HW, Marlow LA, von Roemeling CA, et al. Pathway signature and cellular differentiation in clear cell renal cell carcinoma. *PLoS One*. 2010;5(5):e10696.

60. Deng WG, Jayachandran G, Wu G, Xu K, Roth JA, Ji L. Tumor-specific activation of human telomerase reverse transcriptase promoter activity by activating enhancer-binding protein-2beta in human lung cancer cells. *J Biol Chem*. 2007;282(36):26460-26470.

61. Fu L, Chen W, Guo W, et al. Berberine targets AP-2/hTERT, NF-kB/COX-2, HIF-1alpha/VEGF and cytotoxic-c-caspase signaling to suppress human cancer cell growth. *PLoS One*. 2013;8(7):e69240.

62. Cheng C, Ai Z, Zhao L. Comprehensive analysis of the expression and prognosis for TFAP2 in human lung carcinoma. *Genes Genomics*. 2020;42(7):779-789.

63. Wu H, Zhang J. Decreased expression of TFAP2B in endometrial cancer predicts poor prognosis: a study based on TCGA data. *Gynecol Oncol*. 2018;149:592-597.

64. Wang F, Huang W, Hu X, et al. Transcription factor AP-2beta suppresses cervical cancer cell proliferation by promoting the degradation of its interaction partner beta-catenin. *Mol Carcinog*. 2017;56(8):1909-1923.

65. Oyama N, Takahashi H, Tojo M, et al. Different properties of three isoforms (alpha, beta, and gamma) of transcription factor AP-2 in the expression of human keratinocyte genes. *Arch Dermatol Res*. 2002;294(6):273-280.

66. Friedrichs N, Jager R, Paggen E, et al. Distinct spatial expression patterns of AP-2alpha and AP-2gamma in non-neoplastic human breast and breast cancer. *Mod Pathol*. 2005;18(3):431-438.

67. Friedrichs N, Steiner S, Buettner R, Knoepfle G. Immunohistochemical expression patterns of AP2alpha and AP2gamma in the developing fetal human breast. *Histopathology*. 2007;51(6):814-823.

68. Shen SS, Krishna B, Chirala R, Amato RJ, Truong LD. Kidney-specific cadherin, a specific marker for the distal portion of the nephron and related renal neoplasms. *Mod Pathol*. 2005;18(7):933-940.

69. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747-752.

70. Guedj M, Marisa L, de Reynies A, et al. A refined molecular taxonomy of breast cancer. *Oncogene*. 2012;31(9):1196-1206.

71. Ennour-Idrissi K, Dragic D, Issa E, et al. DNA methylation and breast cancer risk: an epigenome-wide study of normal breast tissue and blood. *Cancers (Basel)*. 2020;12(11):E3088. https://doi.org/10.3390/cancers12113088.

How to cite this article: Raap M, Gierendt L, Kreipe HH, Christgen M. Transcription factor AP-2beta in development, differentiation and tumorigenesis. *Int. J. Cancer*. 2021;1–7. https://doi.org/10.1002/ijc.33558