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Molecular and cellular pathogenesis of pituitary tumors

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Abstract

Pituitary tumors occur sporadically (95%) or as hereditary tumors, either associated with endocrine syndromes (2.5%) or as familial isolated variants (FIPA, 2.5%). In sporadic pituitary tumors, in addition to the known somatotropic *GNAS* mutation, a recurrent mutation of the *USP8* gene was recently detected in corticotropinomas. Thus variable genetic and epigenetic modifications may mostly be responsible for pituitary tumorigenesis. However, these different changes seem to modify common intracellular targets such as distinct tumor suppressors, cell cycle checkpoints or signaling pathways. Thus, recurrently impaired functions in concert with/or recurrently impaired genes may trigger pituitary tumorigenesis. This may also be of relevance for the different steps involved in pituitary tumor progression such as angiogenesis, invasiveness, pituitary tumor senescence and pituitary carcinoma formation.

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Keywords

Sporadic/hereditary pituitary tumors, Whole genome/exome sequencing, USP8 mutation, Pituitary adenoma progression, Pituitary carcinoma, Pituitary tumor senescence.

Abbreviations

AIP, aryl hydrocarbon-interacting protein; BC, bromocriptine; bFGF, basic fibroblast growth factor; cAMP, cyclic adenosine monophosphate; CABLES1, Cdk5 and ABL enzyme substrate 1; CCND2, cyclin D2; CDK8, cyclin dependent kinase 8; DAPK1, death associated protein kinase 1; DPCR1, diffuse panbronchiolitis critical region 1; EGFL7, EGF-like domain multiple 7; EGFR, epidermal growth factor receptor; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; EZR, ezrin; FIPA, familial isolated pituitary adenomas; GH, growth hormone; GHRH, growth hormone releasing hormone; GNAS, gene encoding the alpha-subunit of stimulatory G Protein; GPR, G-protein coupled receptor; HIF-1, hypoxia-inducible factor 1; LRRC50 = DNAAF1, dynein axonemal assembly factor 1; MEN, multiple endocrine neoplasia; MGMT, O-6-methylguanine-DNA methyltransferase; MMP, matrix metalloproteinase; NEBL, nebulette; NDRG4, N-myc down-regulated gene family member 4; NFPA, nonfunctioning pituitary adenoma; NR3C1, nuclear receptor subfamily 3 group C member 1; OIS, oncogene-induced senescence; PCDH15, protocadherin related 15; PDGFD, platelet-derived growth factor D; PKA, protein kinase A; PKC, protein kinase C; PI3K, phosphatidylinositol 3-kinase; PRDM2, PR domain zinc finger protein 2; PRL, prolactin; PTTG, pituitary tumor transforming gene; PTEN, phosphatase and tensin homolog; RB, retinoblastoma; RSUME, RWD-domain-containing sumoylation enhancer; SA-β-gal, senescence-associated β-galactosidase; SMOX, spermidine oxidase; SSTR5, somatostatin receptor 5; SYTL3, synaptotagmin-like protein 3; TGF-α, -β, transforming growth factor-α, -β; TIMP2, tissue inhibitor of metalloproteinase 2; USP8, ubiquitin-specific protease 8; VEGF-A, vascular endothelial growth factor-A; X-LAG, X-chromosome-linked acrogigantism; ZAK, Zipper sterile-α-motif kinase; ZNF676, zink finger protein 676.

Introduction

The pathogenesis of pituitary tumors, the most common intracranial neoplasia, is still only partly understood. The recent application of techniques like whole genome/exome sequencing has led to a considerable progress in understanding the genetic background of pituitary tumors but still many questions remain open. The present review gives a brief overview about the important current findings in molecular and cellular pathogenesis of pituitary adenomas and carcinomas.

Pituitary tumors

In general, pituitary tumors can be divided into two groups, sporadic tumors (>95%) and hereditary ones (<5%), which develop within distinct complex neuroendocrine syndromes [1] or as isolated familiar forms (Familiar Isolated Pituitary Adenoma, FIPA) [2] affecting only the pituitary.

Hereditary pituitary tumors

An overview about hereditary pituitary tumors (Table 1) shows that different underlying mutations lead to the formation of distinct pituitary tumor subtypes suggesting that the affected proteins preferentially impair specific endocrine cell types of the anterior pituitary [1]. In most cases it is unclear through which mechanism the impaired proteins induce the formation of the tumors. For instance in case of MEN1, in which menin, a multifunctional protein with multiple interactions with transcription factors, cell signaling components etc. is impaired, it is not clear why preferentially prolactinomas are induced [3]. In case of Carney Complex, it is

Table 1

Overview about hereditary pituitary tumors (germline mutations).

Syndrome	Affected *Gene*/Protein	Impaired functions	Penetrance[a]/Pituitary adenoma types
MEN1	*MEN1* (AD), menin	Loss of tumor suppressor function	30–40%; mostly prolactinomas
MEN4	*CDKN1B* (AD), cyclin-dependent kinase inhibitor $p27^{Kip1}$	Impaired cell cycle control, impaired MAPK/PI3K interaction	High for pituitary tumors; mostly somatotropinomas
Carney Complex	*PRKAR1A* (AD), regulatory R1α subunit of PKA	Increased PKA activity	80%; somatotroph hyperplasia and somatotropinomas
DICER1	*DICER1* (AD), endoribonuclease	Impaired miRNA processing	<2%; corticotroph pituitary blastoma
Pheochromo-Cytoma Paraganglioma Syndrome	*SDHX* (AD), subunits A, B, C or D of SDH	Impaired respiration, enhanced metabolic rates	very low; mostly prolactinomas
FIPA/AIP[b]	*AIP* (AD), aryl hydrocarbon-interacting protein	Over-activation of the cAMP pathway	30%; somatotroph adenomas (55%), prolactinomas (25%), others (20%)
FIPA/X-LAG[c]	*GPR101* duplication, orphan G protein- coupled receptor GPR101	Over-stimulation of cAMP pathway; elevated GHRH	100%; somatotroph hyperplasia and somatotropinomas

Abbreviations: AD, autosomal dominant; AIP, aryl hydrocarbon-interacting protein; FIPA, familial isolated pituitary adenomas; MAPK, mitogen-activated protein kinase; MEN, multiple endocrine neoplasia; PI3K, phosphoinositide 3-kinase; SDH, succinate dehydrogenase; X-LAG, X-chromosome-linked acrogigantism.

[a] Only for pituitary tumors; not for other syndrome associated tumor types.

[b] The AIP gene is mutated in 25% of FIPAs; the underlying mutations in the vast majority of FIPAs are still unknown.

[c] Microduplication of Xq26.3 is a rare entity (<1%) in FIPAs but due to early childhood onset of somatotroph hyperplasia/somatotropinomas, X-LAG is responsible for 10% of all cases of gigantism.

thought, that the impairment of the R1α subunit and the thus over-activated cAMP/PKA signaling pathway is responsible for the predominant development of somatotropinomas. An impairment of the cAMP/PKA pathway may also play a role in the predominant development of somatotropinomas in *AIP* mutation associated FIPAs [2]. It is speculated that impaired interactions of mutated AIP with phosphodiesterases or with the somatostatin action mediating inhibitory G-protein leads to an over-activation of the cAMP-PKA signal pathway [4,5]. The over-stimulation of this pathway is also supposed to be responsible for elevated GH production in gigantism causing X-LAG, in which the orphan G-protein coupled receptor GPR101 specifically induces childhood-onset somatotropinomas [6]. However, as recently an expression of GPR101 in GHRH producing hypothalamic neurons has been reported, it has been speculated that over-expression of hypothalamic GPR101 may be responsible for the enhanced GHRH levels seen in patients with X-LAG [7]. This suggests that increased circulating GHRH contributes to somatotroph hyperplasia and somatotropinoma formation in X-LAG.

Sporadic pituitary tumors

Sporadic pituitary tumors arise from the different endocrine anterior pituitary cell types after neoplastic transformation by monoclonal expansion. Different chromosomal loci have been identified that seem to be altered and associated with pituitary tumor formation [8]. In a genome-wide association study in a large cohort of pituitary adenoma patients (n in total = 3313 patients) 3 common susceptibility loci (10p12.31, 10q21.1, 13q12.13) have been identified [9]. Putative tumorigenic genes located in these loci are *NEBL*, *PCDH15* and *CDK8*. The latter encodes the cyclin-dependent kinase 8, which is part of the Wnt/β-catenin pathway that is often impaired in pituitary tumors [9]. To further identify the genetic background of the tumors, whole genome or exome sequencing studies have recently been performed for all major types of pituitary tumors.

In this context, an important progress has been made with the recent detection of recurrent gain-of-function mutations in the *USP8* gene encoding ubiquitin-specific protease 8 (USP8) in patients with Cushing's disease [10]. About 30–40% (up to more than 60% in one study) of corticotropinomas in adolescent [10–13] or pediatric patients [14] and patients with Nelson tumors [15] have mutated *USP8*, whereas in silent corticotropinomas *USP8* mutations are lacking [13]. Other types of pituitary tumors have no mutated *USP8* suggesting that the mutations are specific for corticotropinomas. Interestingly the mutations seem to be primate-specific, as in a big cohort of dogs with Cushing's disease no *USP8* mutations were found [16].

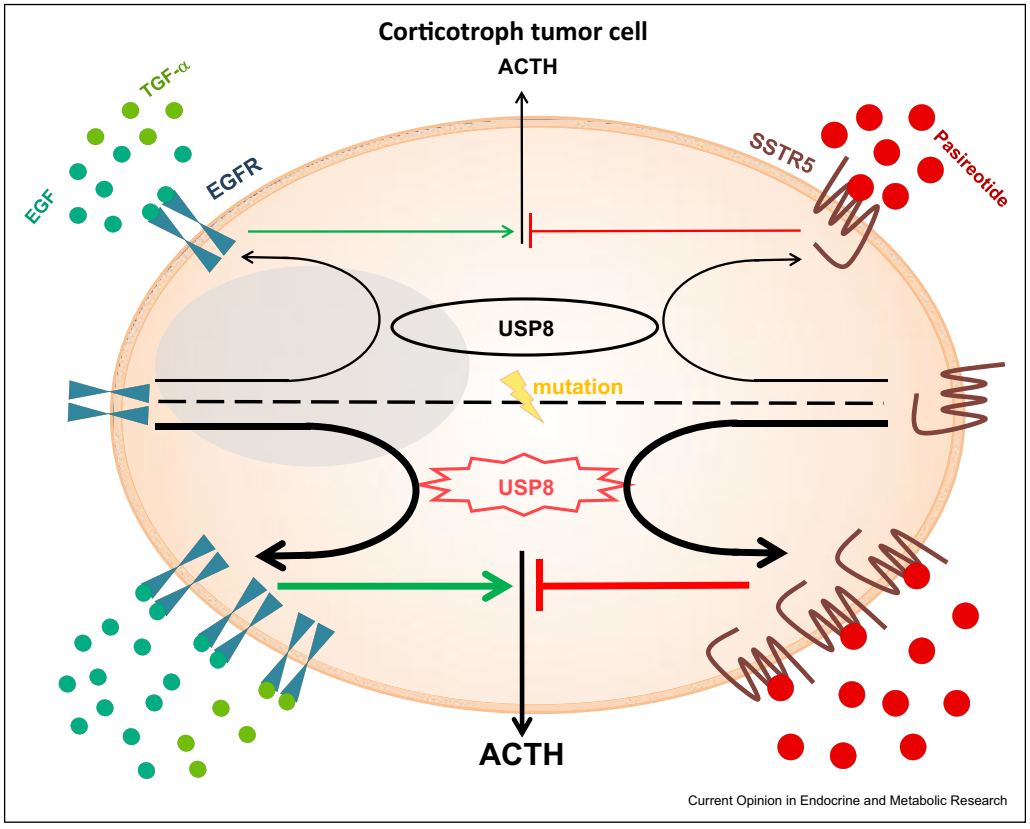
USP8 is involved in the ubiquitination/deubiquitination process which is a mode of post-translational protein modification to regulate the cellular expression and thus

the function of the target proteins [10]. In a complex process specific proteins (receptors, signaling proteins, transcription factors etc.) are ubiquitinated and then lysosomaly degraded or they are rescued from degradation by deubiquitination. In the latter process, USP8 is crucially involved and as the mutation leads to an increased activity of USP8, corticotropinomas with mutated USP8 exhibit more stable or higher levels of proteins regulated by ubiquitination/deubiquitination. Figure 1 shows the functional consequences of USP8 mutations for two putative targets of USP8, namely EGFR [10] and SSTR5 [12], and their role in corticotropinoma pathophysiology and pharmacology.

As only *USP8* was recurrently mutated in corticotropinomas, the majority of these tumors may have a variable genetic background. Very recently, loss of function mutations of the *CABLES1* gene have been found in 4 corticotropinomas from a cohort of 146 pediatric and 35 adult patients, two in children and two in young adults [17]. CABLES1 protein is a glucocorticoid-induced negative regulator of cell growth. The mutated CABLES1 protein has lost its inhibitory action on corticotropinoma cell growth, which may explain that all affected patient developed corticotroph macroadenomas [17].

Recent whole genome and exome studies in somatotropinomas have identified more than 120 somatically mutated genes in these tumors but only the *GNAS* gene was recurrently mutated [18,19]. Activating *GNAS* mutations had already been detected in 1987 and the recent studies confirmed that approximately 30% of the somatotropinomas are affected [18,19]. The *GNAS* gene encodes the regulatory α-subunit of a stimulating G-protein and the mutation changes the a-subunit into a constitutive active form inducing an over-activation of the adenyl cyclase and thus the cAMP/PKA signaling

Figure 1



Consequences of USP8 mutations in corticotropinoma cells. The expression of tyrosine kinase receptor EGFR and the somatostatin receptor 5 (SSTR5) is in part regulated by balanced ubiquitination (receptor degradation) deubiquitination (receptor rescue) processes. The mutation of USP8 leads to enhanced receptor deubiquitination and thus to an enhanced recycling and expression of EGFR and SSTR5 in USP8 mutated corticotropinoma cells, which has recently been demonstrated. In case of elevated EGFR expression, the ACTH-stimulating effects of the epidermal growth factor (EGF) and of the transforming growth factor-α (TGF-α), whose actions are mediated through the EGFR, are enhanced and may contribute to the excessive ACTH production. The elevated SSTR5 expression might explain why USP8 mutant corticotropinomas are mostly smaller than those without mutation, as the growth inhibitory effect of somatostatin is stronger in USP8 mutated tumor cells. Moreover, the elevated SSTR5 levels may also explain why corticotropinomas with USP8 mutation respond better to the treatment with the somatostatin analog pasireotide, which exerts its growth and ACTH inhibitory effects mainly through the SSTR5.

pathway [18,19]. Interestingly, in a cohort of 36 somatotropinomas, 7 different mutated genes were identified whose gene products are associated with the cAMP pathway suggesting that this signaling cascade is a susceptibility hotspot for the genesis of somatotropinomas [18]. In the same study, 11 mutated genes were identified whose products are involved in calcium signaling indicating that disturbances of this pathway might also play a role in somatotropinoma tumorigenesis [18].

In other types of pituitary tumors, no recurrent mutations could be found in whole genome/exome studies. In thyrotropinomas, only single somatic mutations in individual tumors were found [20]. Two of the mutated genes, *SMOX* and *SYTL3* are linked to other types of cancer such as gastric and prostate cancer (*SMOX*) or gall bladder cancer (*SYTL3*) whereas the other mutated 4 genes (*CWH43*, *FSCAN23*, *ASTN2*, *R3DHM2*) have unknown roles [20].

A whole exome sequencing study performed in bromocriptine (BC) responsive and non-responsive prolactinomas identified 10 different mutated genes in single tumors [21]. An inactivating mutation of the *PRDM2* gene leading to the down-regulation of the tumor suppressor RIZ was found in a BC-resistant prolactinoma. RIZ mRNA and protein down-regulation was also found in BC-resistant lactotroph adenomas without *PRDM2* mutations suggesting that this factor could play a general role in determining BC-resistance in prolactinomas [21].

In a series of 7 nonfunctioning pituitary adenomas (NFPAs), whole exome sequencing identified no recurrent gene mutations but 24 different genes with somatic mutations (1−7 mutations per tumor) [22]. Candidate genes associated with cancer were *PDGFD*, *NDRG4* and *ZAK* encoding proteins that act as angiogenic or growth factors, as cell cycle regulators or as tumor suppressors in different types of cancer. However, when trying to validate the mutations of the above mentioned genes in a larger set of NFPAs, no mutations of these genes were found in any of the tumors [22].

A genome-wide study in unselected pituitary adenomas (n = 125) confirmed the recurrent mutations of *USP8* in corticotropinomas and of *GNAS* in GH-producing adenomas. Moreover, mutated *MEN1* was found in 2 out of 15 GH/PRL producing adenomas and mutated *NR3C1* (encodes the glucocorticoid receptor) was found in 2 out of 20 corticotroph adenomas [23].

Epigenetic modifications

In contrast to other solid tumors only very few genetic alterations were found by whole exome/genome sequencing in pituitary adenomas. Therefore it is speculated that epigenetic changes may play an important role in pituitary tumorigenesis [24]. Epigenetic alterations affect the transcription of genes by promoter methylation/de-methylation or histone methylation/demetylation and histone acetylation/de-acetylation or impair the translation of mRNA through interference with microRNA (miRNA) [24]. During the past decade many factors have been identified in pituitary adenomas which over-expressed or down-regulated due to epigenetic modifications of DNA or histones. More detailed analyses of the epigenetically altered factors have shown that many of them are involved in cell cycle regulation [25] and that finally the different epigenetically modified factors have a common target, namely the tumor suppressors RB or p53, whose downregulation is thought to play an important in pituitary tumorigenesis [25]. Also in case of aberrantly expressed miRNAs, many of them target components regulating the cell cycle in pituitary tumor cells indicating this kind of epigenetic modification will also influence and stimulate the proliferation of the adenoma cells [26,27]. This suggests that instead of looking for individual epigenetic alterations and their consequences efforts should be made to bring the different epigenetic modifications into a context and to identify - by creating landscapes of epigenetically modified proteins - the main targets of the individual epigenetic alterations such as oncogenes, tumor suppressors or other tumorigenic key factors.

Pituitary tumor progression

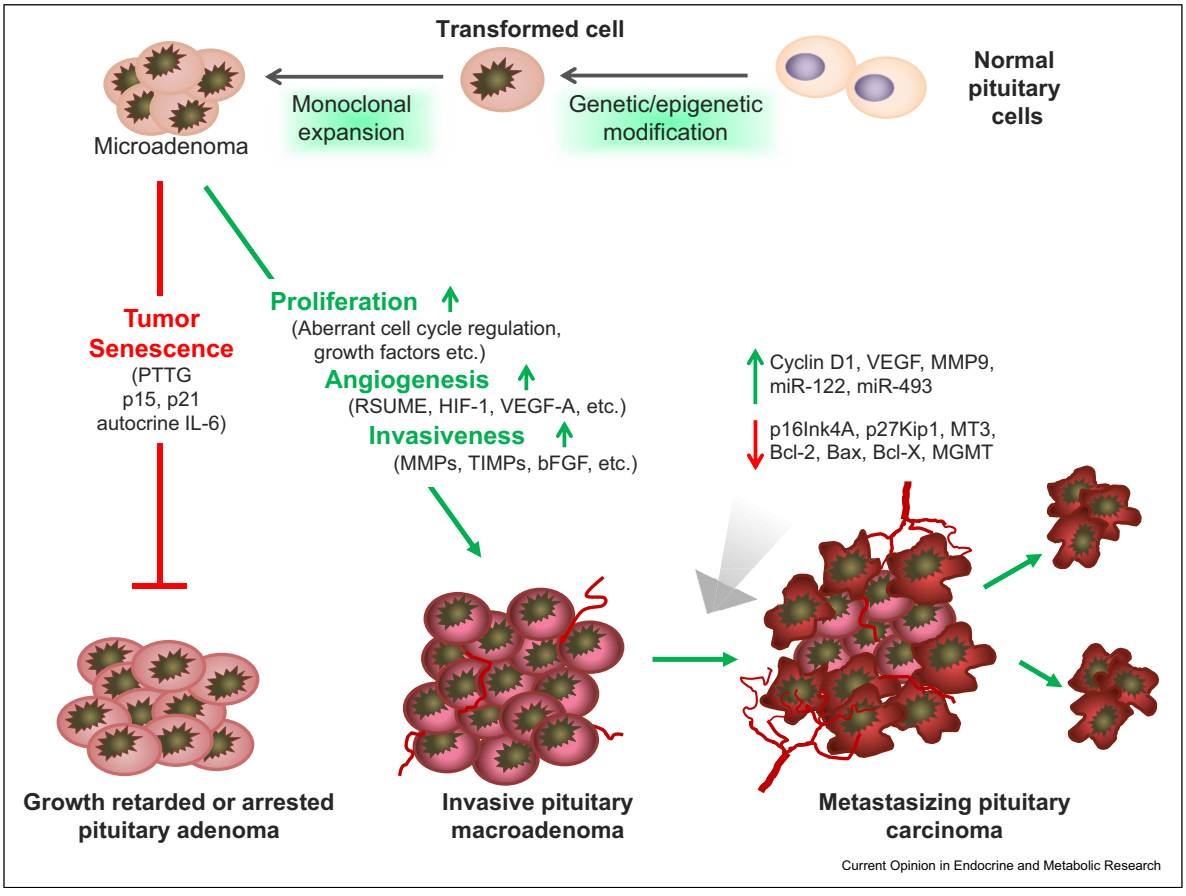
After neoplastic transformation, the further monoclonal expansion of pituitary adenomas occurs very slowly (proliferation index <1%) and is dependent on neovascularization through angiogenesis if the adenomas have reached a critical size (approx. 2 mm). Angiognesis is induced by hypoxia and coordinated by HIF-1, the master trigger of the production of multiple factors that are involved in sprouting of vessels into the expanding tumor, a process that involves also intercellular matrix degradation. Factors related to the latter process such as cell matrix degrading enzymes and their regulators, may link neovascularization with pituitary tumor invasiveness a process describing the penetration of structures surrounding the pituitary by the tumor cells. Many factors that are related to pituitary angiogenesis are also aberrantly expressed in invasive vs. non-invasive adenomas [28], which has recently been confirmed for known factors such as bFGF and MMP14 [29,30]. Moreover, EZH2, which epigenetically represses genes involved in tumorigenesis, was identified as new stimulator of angiogenesis and invasiveness [31]. The product of the *RWWD3* gene, RSUME, was shown to be increased by hypoxia and to stabilize HIF-1α, inducing the expression of angiogenic factors like VEGF-A [32]. RSUME is up-regulated in pituitary adenomas [33], significantly correlated with HIF-1α mRNA levels and its down-regulation strongly reduced VEGF-A expression [33] and the invasion of pituitary tumor

cells [34]. Further new invasiveness-specific factors in pituitary tumors are different miRNAs [35,36] among them miR-200b (targeting PKCα) [37], miR-106b (targeting PTEN-PI3K/AKT) [38], the miR106b−25 cluster (in invasive corticotropinomas/Crooke's cells) [39], long non-coding RNA C5orf66-AS1 [40] and cyclin B1 [41]. Recent gene expression analysis and whole exome sequencing in invasive vs. non-invasive pituitary adenomas identified differently expressed or mutated genes such as *EZR*, *DPCR1*, *EGFL7*, *LRRC50* and members of the *PRDM* family [42,43]. A transcriptome study specifically in invasive vs. non-invasive corticotropinomas showed that *CCND2*, *ZNF676*, *DAPK1* and *TIMP2* genes are differentially expressed as well as genes associated with TGF-β and G protein signaling pathways, DNA damage response pathways and focal adhesion associated pathways [44]. Altogether these findings show the complexity of processes triggering pituitary tumor invasiveness and much work is needed to identify the underlying mechanisms.

Pituitary carcinomas

In contrast to other solid tumor types pituitary adenomas change very slowly to a more aggressive phenotype and the development of finally lethal pituitary carcinomas which has not only been observed in sporadic [45] but also in hereditary pituitary tumors [46], is extremely rare (<0.1%) [45]. Studies trying to identify pituitary carcinoma-specific factors often fail as these factors are also differently expressed in aggressive pituitary macroadenomas [47]. This was confirmed in a recent meta-analysis of genes being up- or down-regulated in pituitary carcinomas in which only factors

Figure 2



Scheme of the different steps of pituitary tumor progression including some key factors/events. After neoplastic transformation and the monoclonal pituitary tumors grow slowly (proliferation index < 1%) and after passing microadenoma and early macroadenoma state become more aggressive and change to an invasively growing tumor that will finally transform to a metastasizing pituitary carcinoma. The carcinoma-associated aberrantly expressed factors shown in the figure are also differently expressed in well-vascularized and invasively growing aggressive pituitary adenomas. This suggests, that an accumulation angiogenesis/invasiveness-related events is finally responsible for pituitary carcinoma development. The mostly late onset of pituitary adenomas and their extremely slow progression in combination with excellent neurosurgical, radiological and pharmacological treatment options may explain why only very few affected patients develop pituitary carcinomas during lifetime. At microadenoma or early macroadenoma state, pituitary tumor senescence may occur in a considerable proportion of the adenomas which could explain, that in autopsy studies up to 20% of the pituitaries contain small, clinically silent adenomas.

were identified (Figure 2), which were also differently expressed in invasive vs. non-invasive adenomas, in micro-vs. macroadenomas or in poorly vs. densely vascularised pituitary tumors [45]. So far no pituitary carcinoma-specific mutation or epigenetic modification could be identified suggesting that the accumulation of genetic and epigenetic changes associated with increased pituitary tumor aggressiveness will finally lead to development of metastasizing pituitary carcinomas.

Pituitary tumor senescence

Autopsy studies have shown that up to 20% of the elder population is bearing small, clinical inactive pituitary tumors, so called incidentalomas, which has led to speculations about the role of tumor senescence in pituitary adenoma development. Tumor senescence, which occurs mainly in benign tumor types, can be induced by specific cellular stress or by oncogenes (oncogene-induced senescence, OIS) and leads to an irreversible growth arrest of the tumor cells without affecting their functions [48]. Whether pituitary adenomas in autopsy material have undergone tumor senescence or represent adenomas that developed late in life of affected persons is not yet clear and needs to be studied by looking for the expression of tumor senescence-specific markers such as SA-β-gal. In OIS of pituitary adenomas the PTTG oncogene seems to play a crucial role [48,49] and pituitary tumor cell-derived, autocrine acting interleukin-6, as recently experimentally shown *in vitro* and *in vivo*, acts as a crucial trigger of pituitary tumor senescence [50]. Further investigations to elucidate the mechanisms of pituitary adenoma senescence are needed and will probably lead to innovative pharmacological concepts in the treatment of pituitary tumors.

Conclusion

In sporadic adenomas, recurrent mutation are present in about 30% of somatotropinomas (*GNAS* gene) and corticotropinomas (*USP8*) whereas the genetic or epigenetic background of the majority of pituitary tumors is heterogeneous or unknown, which is also the case in hereditary FIPAs, in which *AIP* mutations account for less than a quarter of all cases. There is evidence, that despite of the heterogeneity of the genetic or epigenetic changes there are common targets of the different mutated or epigenetically modified factors such as distinct tumor suppressors (e.g. RB, p53), cell cycle regulating components or signaling pathways (cAMP-PKA cascade) suggesting that in the different pituitary adenomas types recurrently impaired functions in concert with/or recurrently impaired genes play an important role in pituitary tumorigenesis. This concept may also play a role in the determination of the different steps involved in pituitary tumor progression such as angiogenesis, invasiveness, pituitary tumor senescence and pituitary carcinoma formation.

Declaration of interest

None.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

1. Caimari F, Korbonits M: **Novel genetic causes of pituitary adenomas**. *Clin Cancer Res* 2016, **22**:5030–5042.
2. Hernandez-Ramirez LC, Gabrovska P, Denes J, Stals K, Trivellin G, Tilley D, *et al.*: **Landscape of familial isolated and young-onset pituitary adenomas: prospective diagnosis in AIP mutation carriers**. *J Clin Endocrinol Metab* 2015, **100**: E1242–E1254.
3. Vannucci L, Marini F, Giusti F, Ciuffi S, Tonelli F, Brandi ML: **MEN1 in children and adolescents: data from patients of a regional referral center for hereditary endocrine tumors**. *Endocrine* 2017, https://doi.org/10.1007/s12020-017-1322-5.
4. Bolger GB, Bizzi MF, Pinheiro SV, Trivellin G, Smoot L, Accavitti M-A, *et al.*: **cAMP-specific PDE4 phosphodiesterases and AIP in the pathogenesis of pituitary tumors**. *Endocr Relat Cancer* 2016, **23**:419–431.
5. Ibanez-Costa A, Korbonits M: **AIP and the somatostatin system in pituitary tumours**. *J Endocrinol* 2017, **235**:R101–R116.
6. Iacovazzo D, Caswell R, Bunce B, Jose S, Yuan B, Hernandez-Ramirez LC, *et al.*: **Germline or somatic GPR101 duplication leads to X-linked acrogigantism: a clinic-pathological and genetic study**. *Acta Neuropathol Commun* 2016, **5**:56.
7. Daly AF, Lysy PA, Desfilles C, Rostomyan L, Mohamed A, Caberg JH, *et al.*: **GHRH excess and blockade in X-LAG syndrome**. *Endocr Relat Cancer* 2016, **23**:161–170.
8. Bi WL, Horowitz P, Greenwald NF, Abedalthagafi M, Agarwalla PK, Gibson WJ, *et al.*: **Landscape of genomic alterations in pituitary adenomas**. *Clin Cancer Res* 2017, **23**: 1841–1851.
9. Ye Z, Li Z, Wang Y, Mao Y, Shen M, Zhang Q, *et al.*: **Common variants at 10p12.31, 10q21.1 and 13q12.13 are associated with sporadic pituitary adenoma**. *Nat Genet* 2015, **47**: 793–798.
10. Reincke M, Sbiera S, Hayakawa A, Theodoropoulou M, Osswald A, Beuschlein F, *et al.*: **Mutations in the deubiquitinase gene USP8 in Cushing's disease**. *Nat Genet* 2015, **47**: 31–38.
11. Ma ZY, Song ZJ, Chen JH, Wang YF, Li SQ, Zhou LF, *et al.*: **Recurrent gain-of-function USP8 mutations in Cushing's disease**. *Cell Res* 2015, **25**:306–317.
12. Hayashi K, Inoshita N, Kawaguchi K, Ibrahim Ardisasmita A, Suzuki H, Fukuhara N, *et al.*: **The USP8 mutational status may predict drug susceptibility in corticotroph adenomas of Cushing's disease**. *Eur J Endocrinol* 2016, **174**:213–226.
13. Perez-Rivas LG, Theodoropoulou M, Ferrau F, Nusser C, Kawaguchi K, Stratakis CA, *et al.*: **The gene of the ubiquitin-specific protease 8 is frequently mutated in adenomas causing Cushing's disease**. *J Clin Endocrinol Metab* 2015, **100**: E997–E1004.
14. Faucz FR, Tirosh A, Tatsi C, Berthon A, Hernandez-Ramirez LC, Settas N, *et al.*: **Somatic USP8 gene mutations are a common cause of pediatric Cushing disease**. *J Clin Endocrinol Metab* 2017, **102**:2836–2843.

15. * Perez-Rivas LG, Theodoropoulou M, Puar TH, Fazel J, Stieg MR, Ferrau F, *et al.*: **Somatic USP8 mutations are frequent events in corticotroph tumor progression causing Nelson's tumor**. *Eur J Endocrinol* 2018, **178**:59–65.
With the detection of recurrent USP8 mutations in Nelson's tumors it has been shown that all subtypes of clinically active corticotropinomas (except USP8 mutation-negative silent corticotropinmas) are bearing similar proportions (30 to 40%) of these mutations regardless of the age and gender of the affected patients (see also references 10 to 14).

16. Sbiera S, Tryfonidou MA, Weigand I, Grinwis GC, Broeckx B, Herterich S, *et al.*: **Lack of ubiquitin specific protease 8 (USP8) mutations in canine corticotroph pituitary adenomas**. *PLoS One* 2016, **11**:e0169009.

17. Hernandez-Ramirez LC, Gam R, Valdes N, Lodish NB, Pankratz N, Balsalobre A, *et al.*: **Loss-of-function mutations in the CABLES1 gene are a novel cause of Cushing's disease**. *Endocr Relat Cancer* 2017, **24**:379–392.

18. Ronchi CL, Peverelli E, Herterich S, Weigand I, Mantovani G, Schwarzmayr T, *et al.*: **Landscape of somatic mutations in sporadic GH-secreting pituitary adenomas**. *Eur J Endocrinol* 2016, **174**:363–372.

19. Valimäki N, Demir H, Pitkänen E, Kaasinen E, Karppinen A, Kivipelto L, *et al.*: **Whole-genome sequencing of growth hormone(GH)-secreting pituitary adenomas**. *J Clin Endocrinol Metab* 2015, **100**:3918–3927.

20. Sapkota S, Horiguchi K, Tosaka M, Yamada S, Yamada M: **Whole-exome sequencing study of thyrotropin-secreting pituitary adenomas**. *J Clin Endocrinol Metab* 2017, **102**: 566–575.

21. Gao H, Wang F, Lan X, Li C, Feng J, Bai J, *et al.*: **Lower PRDM2 expression is associated with dopamine-agonist resistance and tumor recurrence in prolactinomas**. *BMC Cancer* 2015, **15**:272.

22. Newey PJ, Nesbit MA, Rimmer AJ, Head RA, Gorvin CM, Attar M, *et al.*: **Whole-exome sequencing studies of nonfunctioning pituitary adenomas**. *J Clin Endocrinol Metab* 2013, **98**: E796–E800.

23. * Song Z-J, Reitman ZJ, Ma Z-Y, Chen J-H, Zhang Q-L, Shou X-F, *et al.*: **The genome-wide mutational landscape of pituitary adenomas**. *Cell Res* 2016, **26**:1255–1259.
In a series of different types of pituitary adenomas (125 in total) it was shown that mutations of the GNAS gene (in GH-producing adenomas) and of the USP8 gene (exclusively in corticotropinomas) are the only recurrent mutations in pituitary tumors. The majority of the 412 somatic mutations detected in this study affected single different genes confirming the genetic heterogeneity of pituitary tumors.

24. Ezzat S, Cheng S, Asa SL: **Epigenetics of pituitary tumors: pathogenetic and therapeutic implications**. *Mol Cell Endocrinol* 2017, https://doi.org/10.1016/j.mce.2017.07.011.

25. Zhou Y, Zhang X, Klibanski A: **Genetic and epigenetic mutations of tumor suppressive genes in sporadic pituitary adenoma**. *Mol Cell Endocrinol* 2014, **386**:16–33.

26. Wierinckx A, Roche M, Legras-Lachuer C, Trouillas J, Raverot G, Lachuer J: **MicroRNAs in pituitary tumors**. *Mol Cell Endocrinol* 2017, **456**:51–61.

27. Zhang T, Yang Z, Gao H: **Advancements in the study of miRNA regulation during the cell cycle in human pituitary adenomas**. *J Neuro Oncol* 2017, **134**:253–258.

28. Mete O, Ezzat S, Asa SL: **Biomarkers of aggressive pituitary adenomas**. *J Mol Endocrinol* 2012, **49**:R69–R78.

29. Zhou K, Fan YD, Duysenbi S, Wu PF, Feng ZH, Qian Z, *et al.*: **siRNA-mediated silencing of bFGF gene inhibits the proliferation, migration, and invasion of human pituitary adenoma cells**. *Tumour Biol* 2017, **39**, https://doi.org/10.1177/1010428317704805.

30. Hui P, Xu X, Xu L, Hui G, Wu S, Lan Q: **Expression of MMP14 in invasive pituitary adenomas: relationship to invasion and angiogenesis**. *Int J Clin Exp Pathol* 2015, **8**:3556–3567.

31. Liu B, Pang B, Wang Q, Yang S, Gao T, Ding Q, *et al.*: **EZH2 upregulation correlates with tumor invasiveness, proliferation, and angiogenesis in human pituitary adenomas**. *Hum Pathol* 2017, **66**:101–107.

32. Carbia-Nagashima A, Gerez J, Perez-Castro C, Paez-Pereda M, Silberstein S, Stalla GK, *et al.*: **RSUME, a small RWD-containing protein, enhances SUMO conjugation and stabilizes HIF-1alpha during hypoxia**. *Cell* 2007, **131**:309–323.

33. Shan B, Gerez J, Haedo M, Fuertes M, Theodoropoulou M, Buchfelder M, *et al.*: **RSUME is implicated in HIF-1-induced VEGF-A production in pituitary tumour cells**. *Endocr Relat Cancer* 2012, **19**:13–27.

34. * He W, Huang L, Shen X, Yang Y, Wang D, Yang Y, *et al.*: **Relationship between RSUME and HIF-1α/VEGF-A with invasion of pituitary adenoma**. *Gene* 2017, **603**:54–60.
It is shown that the angiogenesis-regulating factor RSUME is not only playing a role in intratumoral neovascularization but is also inducing invasive growth of pituitary tumors. This further indicates, that pituitary neovascularization and invasive growth are closely related events in pituitary tumor progression.

35. Wu S, Gu Y, Huang Y, Won TC, Ding H, Liu T, *et al.*: **Novel biomarkers for non-functioning invasive pituitary adenomas were identified by using analysis of microRNAs expression profile**. *Biochem Genet* 2017, **55**:253–267.

36. Yu G, Wang H, Yu S, Li C, Bai J, Gui S, *et al.*: **Study on miRNAs' expression for the invasion of pituitary adenomas**. *Turk Neurosurg* 2017, https://doi.org/10.5137/1019-5149.JNT.20760-17.1.

37. Wang Y, Yin X, Zhao L, Li S, Duan J, Kuang R, *et al.*: **MicroRNA-200b inhibits pituitary tumor cell proliferation and invasion by targeting PKCa**. *Exp Ther Med* 2017, **14**:1706–1714.

38. Zheng Z, Zhang Y, Zhang Z, Yang Y, Song T: **Effect of miR-106b on invasiveness of pituitary adenoma via PTEN-PI3K/AKT**. *Med Sci Monit* 2017, **23**:1277–1285.

39. Garbicz F, Mehlich D, Rak B, Sajjad E, Maksymowicz M, Paskal W, *et al.*: **Increased expression of the microRNA 106b~25 cluster and its host gene MCM7 in corticotroph pituitary adenomas is associated with tumor invasion and Crooke's cell morphology**. *Pituitary* 2017, **20**:450–463.

40. Yu G, Li C, Xie W, Wang Z, Gao H, Cao L, *et al.*: **Long non-coding RNA C5orf66-AS1 is down-regulated in null cell adenomas and is associated with their invasiveness**. *Oncol Rep* 2017, **38**:1140–1148.

41. Zhao P, Zhang P, Hu W, Wang H, Yu G, Wang Z, *et al.*: **Upregulation of cyclin B1 plays potential roles in the invasiveness of pituitary adenomas**. *J Clin Neurosci* 2017, **43**:267–273.

42. Lan X, Gao H, Wang F, Feng J, Bai J, Zhao P, *et al.*: **Whle-exome sequencing identifies variants in invasive pituitary adenomas**. *Oncol Lett* 2016, **12**:2319–2328.

43. Chen Y, Chuan HL, Yu SY, Li CZ, Wu ZB, Li GL, *et al.*: **A novel invasive-related biomarker in three subtypes of nonfunctioning pituitary adenomas**. *World Neurosurg* 2017, **100**: 514–521.

44. de Araujo LJ, Lerario AM, de Castro M, Martins CS, Bronstein MD, Machado MC, *et al.*: **Transcriptome analysis showed a differential signature between invasive and non-invasive corticotrophinomas**. *Front Endocrinol (Lausanne)* 2017, **8**:55.

45. * Yang Z, Zhang T, Gao H: **Genetic aspects of pituitary carcinoma: a systematic review**. *Medicine* 2016, **95**:e5268.
In this paper records about pituitary carcinomas were systematically compared for abundant changes in pituitary carcinomas vs. adenomas and a number of factors related to cell cycle control, angiogenesis, invasiveness, apoptosis etc. were found to be up- or down-regulated. As these factors were also aberrantly expressed in aggressive pituitary adenomas, it seems that an accumulation of proliferation-, angiogenesis- and invasiveness-associated factors will finally lead to pituitary carcinoma development.

46. Tufton N, Roncaroli F, Hadjidemetriou I, Dang MN, Denes J, Guasti L, *et al.*: **Pituitary carcinoma in a patient with an SDHB mutation**. *Endocr Pathol* 2017, **28**:320–325.

47. Roche M, Wierinckx A, Croze S, Rey C, Legras-Lachuer C, Morel A-P, *et al.*: **Deregulation of miR-183 and KIAA0101 in**

aggressive and malignant pituitary tumors. *Front Med (Lausanne)* 2015, https://doi.org/10.3389/fmed.2015.00054.

48. Arzt E, Chesnokova V, Stalla GK, Melmed S: **Pituitary adenoma growth: a model for cellular senescence and cytokine action**. *Cell Cycle* 2009, **8**:677–678.

49. Sapochnik M, Fuertes M, Arzt E: **Programmed cell senescence: role of IL-6 in the pituitary**. *J Mol Endocrinol* 2017, **58**: R241–R253.

50. * Sapochnik M, Haedo MR, Fuertes M, Ajler P, Carrizo G, Cervio A, *et al.*: **Autocrine IL-6 mediates pituitary tumor senescence**. *Oncotarget* 2017, **8**:4690–4702.

It was shown *in vitro* and *in vivo* in nude mice, that intratumorally produced, autocrine-acting IL-6 could induce growth suppression of pituitary tumors and that the silencing of intrinsic IL-6 production induced down-regulation of the tumor senescence marker SA-β-gal and re-growth of pituitary tumors. This indicates that IL-6 is crucially involved in pituitary tumor senescence.