Pituitary

Pathogenesis of non-functioning pituitary adenomas

--Manuscript Draft--

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Response to Reviewers:	Dear Editor Thank you for giving me the opportunity to revise the manuscript, which I hope will be considered for publication in Pituitary. The text has been extensively integrated thanks to the illuminating suggestions of the Reviewers. Reviewer #1: This is a comprehensive review of this topic by a well regarded investigator in the field. Regrettably, many new concepts are omitted. several important concerns: Question 1. Author tends to use very old references and not to update the topics. For example section on EGFR and erb ignores recent work in JCI by Fukuoka group, and yet focuses on older ligand binding work. Also, reference 31 is from 2007. Reference 35 has not been validated. Answer 1: I would like to thank the reviewer for highlighting this issue. In keeping with the Reviewer's suggestion, I added the reference to the work of Fukuoka et al. published in JCI in 2011. The latter reference deals with human, canine and mouse ACTH-secreting pituitary adenomas, therefore has not been further used as a source for this review, which deals with non functioning pituitary adenomas. Similarly, in order to follow the Reviewer's indication, reference 31 of the originally submitted manuscript has been removed. Along this line, also reference 35 has been removed. Unfortunately, most of the published evidence on the possible role of EGFR and its ligands in NFPA is quite old. Question 2.First reference (ref 1) is old 2009,please use more recent and more cogent quality review on pituitary tumor pathogenesis in Nature Reviews Endocrinology. This provides a far more compelling platform for this review. See some figures from that work which may be reproduced (with permission). Answer 2: In keeping with the Reviewer's indication I replaced reference 1 of the previous submission with the review by Dr Melmed, a well recognized expert in the field of pituitary adenomas. I opted to provide original figures, more specific with the

	topic of this review, which is the pathogenesis of non functioning pituitary adenomas. The beautiful pictures of Dr Melmed's review are indeed more related to the pathogenesis of pituitary adenomas, in general. Question 3. Description of AIP ignores more recent very important work of the Beckers group--should replace the older ones. Answer 3. In keeping with the Reviewer's suggestion, I included the more recent work of Beckers group indicating the prevalence of NFPA among patients with germ-line AIP mutations. Question 4. Discussion on p53 (reference 26)-is very old and ignores more recent work by Chesnokova et al in PNAS on p53 and pituitary growth. Answer 4: I thank the Reviewer for pointing out this weakness of the review. However, I preferred to quote in the revised review the papers by Chesnokova published in PLOS One and in Molecular Endocrinology, since the paper published in PNAS mainly deals with GH-secreting pituitary adenomas and cell lines. Question 5.SSA receptor profiles were first described by Greenman-please discuss these in light of the older reference 45. Answer 5: In keeping with the Reviewer's indication, I quoted the original papers first describing SSA receptor expression pattern in NFA. Question 6.Stem cell story is very weak. Vankelcom reference ignores recent exciting work by Tabar 2016 and 2017; Studier; Risotti; Antoniades etc etc. This is a very hot area for pituitary tumor pathogenesis and vankelcom work is now outmoded. Also see recent work by Suda in Japan in Nature on this exciting topic. Answer 6. According to the Reviewer's indication I expanded the section on the role of pituitary stem cells in the pathogenesis of pituitary tumors and updated the sources, trying to focus mainly on NFPAs. Question 7. Dattani work on pituitary transcription factors and tumors should be discussed. Answer 7. As indicated by the Reviewer, I quoted the work by the group of Dattani (and others) on pituitary transcription factors and pituitary tumors. Reviewer#2 Question 1) This is a comprehensive review but requires more critical assessments of what is important and what is not Answer 1: In keeping with the Reviewer's indication, at the end of each paragraph I added a comment on the relevance of the findings there illustrated. Question 2) Minor comment regarding the figure : it is not mentioned anywhere in the manuscript where fig should be inserted and does not have a separate legend Answer 2: I thank the Reviewer for having underlined this omission. Figure 1 is now quoted in the revised version of the manuscript at the end of the Introduction paragraph. A separate legend has also been added. Question 3) Also, as title is non-functioning pituitary adenomas, will be helpful to change abbreviations to NFPA, instead of NFPT (see first line of intro) throughout abstract and manuscript. Answer 3: In keeping with the Reviewer's indication I modified the abbreviations for non-functioning pituitary adenoma in NFPA throughout abstract and manuscript.

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ABSTRACT

The pathogenesis of non functioning pituitary adenomas (NFPA) is a complex process involving several factors, from molecular to genetic and epigenetic modifications, where tumor suppressor genes, oncogenes, cell cycle derangements have been demonstrated to play an important role. MicroRNAs (miRNAs) have also been identified as possible players in NFPA tumorigenesis and pituitary stem cells have been investigated for their potential role in pituitary tumor initiation. However, a critical role for paracrine signalling has also been highlighted. This review focuses on the current knowledge on the involvement of these factors in NFPA pathogenesis.

INTRODUCTION

Non functioning pituitary adenomas (NFPA), representing ~30% of anterior pituitary tumors (1), are characterized by the lack of hormonal expression and/or secretion and, as a consequence, by the lack of a related hormonal syndrome. However, this wide group of neoplasms includes a variety of pathological entities, going form the silent tropinomas to the null cell pituitary adenomas, as detailed in the last WHO classification (2). Silent adenomas are considered to secrete pituitary hormone isoforms devoid of any biological activity or to produce very limited amounts of normal pituitary hormones. Null cell adenomas, on the contrary, may ultrastructurally resemble specific pituitary cell types and express pituitary transcription factors, but do not secrete hormonal proteins (3). In addition to immunohistochemical parameters, molecular classifications have been attempted, but are still far for being possibly implemented. Therefore, the pathogenesis of NFPA embraces many hypotheses, that include genetic and epigenetic events, hormonal stimulation, growth factor overproduction, pituitary stem cells derangements and microRNAs (miRNAs) deregulation that might promote tumor growth and proliferation (Figure 1).

Gene mutations

Several clinical syndromes due to germ-line mutations may include the development of pituitary adenomas among their clinical presentation. MEN1 syndrome is classically composed by parathyroid hyperplasia/adenomas, pituitary adenomas and neuroendocrine tumors of the gastro-entero-pancreatic tract. The syndrome is correlated, in the majority of familial cases, to germ-line heterozygous mutations in the *MEN1* gene, located on chromosome 11q13, which encodes for the menin protein (4). Among the pituitary adenomas possibly associated to 15-50% of MEN1 patients, NFPA are quite rare and may display a more aggressive behaviour, similarly to the functioning counterparts (5, 6). MEN4 syndrome represents an other genetic condition causing the development

of a pituitary adenoma in association with different endocrine neoplasms. The syndrome is due to germ-line mutations in the *CDKN1B* gene, encoding for p27Kip1, an important negative regulator of cell cycle progression and a putative tumor suppressor gene. Among MEN4 affected patients ~40% present with a pituitary tumor as second manifestation, including usually indolent NFPA (7). However, no data are available concerning *CDKN1B* mutations in sporadic NFPA, therefore the specific role of p27 deregulation in NFPA pathogenesis remains unclear. Germ-line mutations in the aryl hydrocarbon receptor-interacting protein (*AIP*) gene were found in 15 patients among the 215 AIP mutation/deletion–associated cases reported in an overview of the published literature (8, 9), but have not been described among 10 patients with sporadic NFPA macro-adenomas diagnosed within 40 years of age included in a Brazilian series (10) and among 56 patients with sporadic NFPA included in a Chinese series (11), suggesting that *AIP* mutations might not play an important role in the tumorigenesis of sporadic NFPA. On the contrary, activating somatic mutations of the *PIK3CA* gene have been described in NFPA, including some invasive forms. *PIK3CA* encodes for the catalytic subunit of PI3-Kinase IA, within the AKT signalling pathway (12), which regulates several important pituitary growth pathways, therefore indicating that these alterations may contribute to NFPA development.

In addition to genetic mutations, gene expression may be modified by epigenetic changes. In these settings, promoter methylation importantly regulates gene expression also in NFPA. In particular, the tumor suppressor protein p16, a cyclin-dependent kinase inhibitor encoded by the *CDKN2A* gene, is frequently down-regulated in pituitary tumors, especially in NFPA (13), possibly accounting for a reduced cell cycle control and for unrestrained pituitary cell proliferation. Similarly, a reduced control of programmed cell death through apoptotic mechanisms may be taken into account when considering that the expression of DNA damage inducible gene 45g (*GADD45g*) a p53-regulated gene that negatively regulates pituitary growth, is down-regulated in NFPA due to promoter methylation (14). An other p53-dependent gene, the maternally expressed gene 3 (*MEG3*) which acts as a tumor suppressor gene is down-regulated in pituitary adenomas, especially in NFPA (15), supporting the hypothesis that an enhanced cell survival, in addition to a reduced control of cell proliferation, may promote NFPA growth.

The available literature, therefore, points to epigenetic changes and somatic mutations rather than to germ-line mutations as more likely influencing the development of NFPA, suggesting that genetic predisposition does not play an important role in NFPA pathogenesis.

miRNA

miRNAs are small non coding RNA molecules that, by pairing to the complementary mRNA sequence, negatively regulate post-transcriptional gene expression, having profound consequences on physiological and pathological processes influencing cell growth. Their involvement in pituitary adenoma pathogenesis and their possible role as potential therapeutic targets has been extensively investigated in the last few years (16). Several studies found that miRNAs are differentially expressed in NFPA as compared to normal pituitary, being either over-expressed or down-regulated (17, 18, 19). Several of these deregulated miRNAs map in the imprinted DLK1/MEG3 locus, which displays an onco-suppressor activity (20), as supported by the evidence that one of these down-regulated miRNAs, miR-134, restrains cell cycle progression in G2/M phase in folliculostellate cells originated from a human NFPA. In addition, the differential miRNA expression pattern has been predicted to regulate transforming growth factor beta (TGFβ) signalling pathway (17) and Wee1, a mitotic inhibitor that hampers cell cycle progression, usually expressed at low levels in NFPA (21). In addition, Notch and prolactin signalling have been shown to be deeply regulated by miRNAs in NFPA (22), indicating that miRNAs deregulation has complex functional consequences in these tumors similarly to what demonstrated in other tumors.

The field of miRNA is still rapidly evolving and may provide further important information concerning the possible pathogenetic mechanisms of NFPA, but the available data, so far, are still prelimiary.

Signalling pathways

Similarly to tumors arising in different organs, pituitary tumors, and NFPA as well, may display derangements in several signalling pathways that may participate in pituitary neoplastic transformation. A recent study analyzed the data generated by a microarray study on 14 NFPA (including 4 null cell adenomas and 10 gonadotroph adenomas) compared with 9 normal pituitary glands (23), and found >600 differentially expressed genes, that were capable of correctly differentiating normal from pathological samples after clustering. Gene Ontology analysis and Kyoto Encyclopedia of Genes and Genomes pathway analyses identified several significantly enriched pathways, mainly associated with signalling pathways (MAPK, p53 TGFβ, Jak-STAT), cell-to-cell interaction (cell communication and signalling, cellular components related with extracellular matrix, plasma membrane and collagen) and signal transduction (transcription factor activity, receptor binding) (24). Derangements in the PI3K/Akt/mTOR and Raf/MEK/ERK signalling pathway have been thoroughly investigated, as detailed elsewhere (25), mainly in the eventuality of using mTOR as a therapeutic target (26). It has been previously demonstrated that

p53 mutations are rare in pituitary adenomas (27, 28), while p53 staining is commonly found in NFPA, where it associates with a greater aggressiveness (29), suggesting that this pathway is over-activated and may contribute to pituitary transformation. In keeping with this evidence, it is has been reported that NFPA display activated DNA damage signalling (γH2A.X and ATM) and clusterin-mediated senescence markers (p16 and p15) (30), supporting a role for clusterin, which is abundantly expressed in NFPA, in specifically restraining proliferation of these pituitary tumors. Further work demonstrated that clusterin expression is stimulated by gonadotroph-specific forkhead transcription factor FOXL2 and by PTTG in NFPA, which abundantly express and release clusterin. These data further support the hypothesis that clusterin is important in restraining pituitary cell proliferation by inducing cyclin dependent kinase inhibitors (31), indicating that this pathway may represent a new molecular player in the pathogenesis of NFPA.

TGFβ signalling has been shown to be the target of deregulated miRNAs via Smad3 in NFPA (17), possibly causing a shift of the TGFβ pathway towards alternative signalling including the MAPK cascade, with consequent proliferative effects. Since TGFβ promoter was found un-methylated (as well as MMP-14 gene promoter) in the majority of NFPA (32), this potentially deranged pathway may be actively involved in pituitary transformation. In addition, despite several genes encoding for components of the Jak-STAT signalling pathway were found to be significantly down-regulated (24), STAT3 gene promoter methylation and mRNA expression do not seem to be significantly different in NFPA as compared to other pituitary tumors, indicating that STAT3 may not play an important role in pituitary tumorigenesis (33). Among the differentially expressed genes detected by microarray (23, 24), Epidermal Growth Factor (EGF) and its receptor (EGFR) have been confirmed as de-regulated in pituitary tumors. EGFR aberrant expression may lead to receptor homo- or hetero-dimerization, that turns on the intrinsic receptor tyrosine kinase and consequently activates intracellular signalling cascades strongly involved in neoplastic transformation in many tissues, including pituitary (34, 35). The majority of the investigated NFPA in many studies show EGFR expression (investigated by different means) (36, 37, 38, 39, 40, 41, 42). One of these studies also showed that EGF binding is higher in invasive adenomas and especially in those invading the sphenoid sinus (42), suggesting that EGFR may represent a marker of pituitary tumor aggressiveness. In addition, the evidence that NFPA may also express and secrete EGFR ligands supports the hypothesis of the presence of an autocrine-paracrine loop. Indeed, the use of neutralizing antibodies against EGF was capable of reducing the growth promoting activity of conditioned medium deriving from NFPA in primary culture (43). In similar settings, EGF was found to promote DNA synthesis and increase cell number (44). In addition, in the gonadotroph tumor cell line, the alphaT3-1 cells, GnRH-induced MAPK pathway activation could be blocked by

an EGFR inhibitor (45), indicating a cross talk between the two pathways. However, a clear role for EGFR signalling in NFPA pathogenesis is yet to be clarified.

The expression of the estrogen receptor (ER) and its variants in normal and neoplastic pituitary has been demonstrated many years ago (46) and recently confirmed (23, 24). ER1 expression was found to be higher in NFPA as compared to functioning pituitary adenomas in patients younger than 50 years (47). A correlation was found between ER1 expression and dopamine receptor subtype 2 expression, but not with tumor diameter and/or extension (48). Besides modulating anterior pituitary hormone production, estrogens are potent cell mitogens, being implicated in tumor development and growth. Therefore, they could be involved in NFPA development, as well, at least during fertile life. Somatostatin receptor (SSTR) subtypes expression profile has been investigated in NFPA (49, 50), which appear to mainly express SSTR3, while SSTR2 and SSTR5 are expressed at a lower frequency. These findings, besides possibly explaining the relative inefficacy of octreotide and lanreotide (which mainly bind SSTR2 and SSTR5) in the medical therapy of NFPA, may suggest that SSTR3 might be involved in modulating NFPA growth.

The components of the complex pathways involved in the development of normal pituitary gland may display genetic variations, possibly influencing also the development of pituitary hyperplasia and adenomas (51). The SOX2 transcription factor is an early marker of progenitor cells, required for normal pituitary proliferation, and its expression decreases as pituitary cells differentiate (52). SOX2 may influence cell cycle progression by interacting with Wnt signalling, which, in turn, affects pituitary development by controlling the proliferation of Rathke's pouch precursors and the differentiation of PIT-1 positive cells (53). In the animal model, Wnt over-activation causes pituitary cell proliferation, leading to hyperplasia (54). Along this line, heterozygous SOX2 mutations are associated with hypopituitarism and severe ocular phenotypes with small/normal pituitary gland. However, two unrelated patients with SOX2 haploinsufficiency developed cystic pituitary tumors before 20 years of age, suggesting a possible role for the reported SOX2 mutations in the development of pituitary tumors. The truncating mutations displayed by these two patients cause SOX2 loss of function and altered sub-cellular localization. In addition, in vitro studies showed that the mutant SOX2 proteins are unable to repress β-catenin transcriptional activity (55), with consequent β-catenin increased activity. β-catenin overactivating mutations are very frequent in human adamantinomatous craniopharyngiomas (56), while Wnt inhibitors are downregulated in pituitary tumors, including NFPA (57). Indeed, pituitary tumors, and especially NFPA, display reduced levels of Wnt inhibitory factor-1 (WIF1) as compared to normal pituitary, supporting the hypothesis that Wnt pathway is important in pituitary tumorigenesis.

Among signalling pathway derangements, p53 and Wnt signalling are more supported by current published evidence as important determinants in NFPA development, and further studies in this field will likely unravel important molecular mechanisms for NFPA pathogenesis.

Stem cells

The capacity of the pituitary gland to regenerate after injury in adult life is quite limited and may involve differentiating processes of undifferentiated pituitary stem cells/progenitor cells into specialized cells, possibly involving the activation of a senescence-associated secretory phenotype (58). As previously highlighted, senescence plays an important role in preventing the development of pituitary adenomas in mouse models (59) and may regulate stem cells expansion also by acting in a paracrine fashion (58). Pituitary stem cells have been demonstrated also in pituitary adenomas, including NFPAs (60, 61): these cells, similarly to pluripotent stem cells, display clonogenic ability in vitro, express stem cell markers, are multipotent and resist to cytotoxic drugs, being also capable of forming tumor spheres and generating tumors in nude mice (62, 63). The role of pituitary stem cells in maintaining and supporting pituitary adenoma development is still the focus of intensive studies. Recently, Peverelli et al. (64) provided evidence that NFPA contain progenitor/stem-like cells that express stem cell specific markers, as well as pituitary embryonic transcription factors involved in gonadotrope differentiation. Sphere-forming cells displayed long-term proliferation ability and tumorigenic potential in animal models, where they showed an invasive behavior and pro-angiogenic activity. In addition, the Authors showed that the proliferation rate of NFPA stem cells may be reduced by dopamine and somatostatin receptor agonists, underlining the potential therapeutic application of these drugs also in the medical therapy of NFPA, as supported also by an independent study (65). Therefore, pituitary stem cells may play a major role both in the initiation process of pituitary tumorigenesis as well as in pituitary tumor growth (66). This hypothesis is further supported by the evidence that Notch pathway components, participating to stem cell signaling and to pituitary embryonic development, are differentially expressed in pituitary adenomas. It has been indeed shown that *Notch3* and *Jagged1* are over-expressed in human NFPA as compared to normal pituitary gland (67, 68) and that NOTCH3 protein is present in the cytoplasm and membrane of tumor cells that are scattered and isolated within the tumor (69). Further studies are necessary to understand the relationship between pituitary tumor initiating cells and pituitary stem cells that provide support for tumor growth and development (70).

Angiogenesis

Angiogenesis is a complex process induced by angiogenic stimuli to form new blood vessels from pre-existing vessels in order to provide for oxygen and substrates in neoplastic tissues. Several angiogenic factors have been demonstrated to be expressed at pituitary level, both in normal and in adenomatous tissues (71). Along this line, vascular endothelial growth factor (VEGF) and its receptor (VEGF-R1) were found increased in NFPA as compared to normal pituitary (72), suggesting that they may play a role in pituitary angiogenesis and therefore in pituitary tumor growth, providing the basis of a possible autocrine loop. In addition, further evidence show that VEGF signalling may directly impact NFPA cells by promoting cell viability (73). As a consequence, therapeutic approaches potentially reducing pituitary VEGF production, such as somatostatin analogues and dopamine receptor agonists may help in controlling NFPA growth (74, 75). The PI3K/Akt/mTOR pathway has also been demonstrated to be involved in angiogenesis. In the study by Trovato et al. (76), pAKT staining was found in almost half of the 12 NFPA investigated cases, where the microvascular distribution, also related to tumor size, suggested that pAKT signaling may play an important role in tumor growth and angiogenesis. However, mTOR does not seem to modulate VEGF effects on NFPA angiogenesis, since its blockade does not affect VEGF secretion, although it hampers the stimulatory effects of IGF-1 on this parameter (26). In addition to "classic" neoangiogenesis, the neoplastic pituitary gland was found to be a site of "vasculogenic mimicry", as an additional mechanism for neoplastic blood perfusion due to new functional vascular channels lined by neoplastic cells and not by endothelial cells (77). Normal pituitary does not display vasculogenic mimicry, that was found in almost half of the 49 evaluated NFPA cases, although the Authors were unable to demonstrate any correlation with patients clinical characteristics and outcome (78).

Angiogenesis is one of the most potent triggers of tumor development, and NFA are not different from other tissues. However, the gathered data do not allow to conclude that angiogenic factors may represent the initiating event in NFPA, but rather may facilitate pituitary tumor survival and expansion, similarly to what observed in other tissues.

Immune check points

In the last few years the knowledge concerning the regulation of cell-mediated immune responses in cancer tissues has evolved exponentially. In particular, the proteins that negatively regulate T cell activation, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1)/programmed death ligand-1 (PD-L1) have been the focus of much interest due to the potential therapeutic application of specific drugs. Tumor infiltrating lymphocytes express PD-1

that recognizes its ligand, PD-L1, expressed by tumor cells or antigen-presenting cells (79). The binding of PDL1 to PD1 (an "immune checkpoint") abrogates cancer cell killing by activated lymphocytes (80, 81). A recent study has shown that NFPA display lower PD-L1 mRNA and protein levels as compared to functioning pituitary tumors. In addition, NFPA showed an increased PD-1 expression and a reduced lymphocyte infiltration, as compared to the functioning pituitary tumors, suggesting that NFPA may evade immune surveillance by triggering this checkpoint. These data support the hypothesis that NFPA growth may be facilitated by the presence of an adaptive immune resistance mechanism (82). On the other hand, treatment with immune check point inhibitors frequently leads to the development of hypophysitis (83), indicating that the pituitary environment is especially sensitive to immune-related deregulation.

CONCLUSIONS

The pathogenesis of NFPA may involve different factors, either genetically determined or due to external influences. The research in this field is hampered by the lack of satisfactory in vitro and in vivo models (i.e. human pituitary adenoma cell lines and animal models) that have been pivotal in many other fields to understand the pathogenesis of the disease. Most of the information gained by means of basic studies has been and is expected to become the basis for the development of innovative therapeutic approaches and of novel diagnostic markers, translating into early detection of these tumors and more effective treatment in human patients in the next future.

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FIGURE LEGEND

Figure 1: Current hypotheses on the pathogenesis of non-functioning pituitary adenomas.

Figure

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Figure 1