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Pituitary Adenomatous Transformation of Subclonally Derived Proliferative Centers

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Abstract: Proliferative centers appear a possible mechanistic pathway of evolutionary change involving anterior pituitary adenomatous transformation. It appears significant that although pituitary adenomas are monoclonal and apparently unrelated to hyperplasia, there evolves a series of multistep transformations in the generation of excessive hormonal secretory activity. It is in terms of glandular and cellular secretion that one would recognize anterior pituitary adenomas largely as proliferative centers that predetermine clonality of cell multiplication. It might be largely because of change arising in the setting of initially established proliferative centers that subsequently respond in a feed-forward fashion to hormonal influences that secretory activity would prove determinant in the establishment of clones of adenomatous cells. It is in the setting of evolving selectivity in cell proliferative centers that involves assumption of secretory activity that hormonal feed-forward effects subsequently evolve as autonomous cellular propagation of both proliferative and secretory activity. Anterior pituitary adenoma is an alternative pathway to hyperplasia in terms of autonomous proliferative centers clonally selected in terms not only of cell division but particularly of secretory responsiveness to hormonal effect.

Key words: Transfarmation, pituitary, proliferative, adenomatous

INTRODUCTION

Pituitary hyperplasia and adenoma as integral lesions in development: Monoclonality appears an alternative function to hyperplasia, particularly involving pit1 positive cells[1], subsequently modified by adenomatous transformation of proliferative patterns of tumor cell behavior[2-6]. One might speak of how groups of cells constitute not only clones but also a derived sequence of subclones undergoing evolving neoplastic development. It might be significant to consider how hyperplasia, and also double pituitary adenomas[7], typify attributes of a polyclonality that specifically evolves to monoclonal adenomatous proliferation in the anterior pituitary[8]. One might further recognize a full set of attributes in adenoma development that are selectively subcloned to develop as an anterior pituitary lesion with possible subsequent malignant transformation. The only activating mutations identified are gsp mutations with constitutive activation of cAMP pathway[9].

Such evolving hyperplastic proliferation would appear distinct from radical transformation of polyclonality not only as a series of subclonal proliferations but particularly as a monoclonal activation pattern involving proliferation centers within groups of pituitary cells.

A concept of proliferative centers that evolve largely as transformed susceptibility towards multiple but selective subclonality might further reinforce a tendency for neoplastic establishment within an otherwise hyperplastic field of proliferation.

It is also with regard to hyperplasia as a constitutive event in the evolving biology of a lesion in anterior pituitary cells and also as an alternate tendency for clonal subset evolution that subclonality would constitute a distinctive phenomenon in its own right. The occasional development of multiple pituitary adenomas emphasizes the role also of extrahypophysial factors in clonal expansion of genetically altered cells[10]. One might speak of subclonal evolution as distinct both from proliferation or subsequent derivation of given sets of cells.

It is perhaps in the latter definition of evolving consequences of subclones of proliferating cells that monoclonality would distinctly characterize an anterior pituitary adenoma that is subdivisible in terms of various proliferative centers locally and regionally. Proliferative centers would further characterize evolving subclonality as an initial oligoclonal derivation of single or multiple groups of cells otherwise characterizing hyperplasia or adenomatous evolution in the anterior pituitary.

It might be significant to recognize anterior pituitary adenomas largely as subclonal proliferative centers that multifocally evolve on a background of distinctively characterized hyperplastic proliferations. Indeed, hyperplasia in subclonal adenomatous evolution would be expressions of a further change in proliferative centers that come to determine subclonality of a lesion. Thus, hypothalamic peptides might promote initiation of a genetic event that facilitates clonal expansion of the

transformed cell[11].

Subclonal derivation would be the basic mechanistic determinant in both further characterization of evolution of a hyperplastic lesion and of the adenomatous evolution of an apparently integral lesion. One might specify the anterior pituitary as a relative percentage of subclonal proliferating cells that further evolve as zonal proliferative activity both in terms of polyclonal and monoclonal attributes.

Distinction of a variable component set of monoclonally derived proliferating cell centers would perhaps account for potentiality for evolution of anterior pituitary lesions both as either an integral hyperplastic or adenomatous proliferation.

Apoptotic potential further redefines neoplastic transformation: Oncogene activation versus transforming ability appears largely a functional attribute of transcriptional activity within cells that initiate proliferation[12]. Proliferation of cells perhaps constitutes an essential evolutionary process in biologic transformation of cells that may subsequently undergo malignant change.

In view of essential consequences of events emanating in response to transcriptional stimuli, it might be significant that tumor cells are aneuploid even in terms of mechanisms governing oncogene transcription. It is perhaps particularly in terms of an imbalance between sets of chromosomes that evolutionary pathways could implicate amplification of proto-oncogenes as a malignant transformation series of events.

One might view pituitary tumors as the development of proliferative potential directed towards subsequent progression of possible aneuploidy but in strict contradistinction to other evolving consequences of progressive proliferation. Increasing allelic loss develops with tumor dedifferentiation and malignant transformation[13].

It might be a consequence of a proliferative attribute largely arising in terms of various multiple pathways that induce genes to amplify that one might subsequently determine pathogenesis in transformation akin to unlimited growth potential. Simple numerical chromosomal aberrations may characterize some pituitary adenomas[14].

Hormonal consequences of cellular effects that develop in terms of a pituitary adenoma would appear self-sustaining, potentially bridging cellular growth and hyperplasia and also evolving adenomatous transformation[15]. Autonomous cell mitosis would incorporate variable susceptibility towards apoptosis that redefines the neoplastic transformation event in the first instance.

Neovascularization induced by growth factors perpetuates pituitary cell proliferation: A stimulus for growth and particularly for mitotic activity appears a centrally operative mechanism in the initiation of pituitary adenoma formation [16]. Within such a context, various growth factors[17] would implicate the realization of variable factors that pathogenetically promote expression of splice variants of their respective receptors. In pituitary tumors, growth factors or their receptors may be overexpressed at variable levels[18].

An ongoing interactive and dynamic participation of such growth factor splice variants would involve a primary pituitary cell abnormality that potentiates the ongoing stimulation of various pathways as represented especially by Vascular Endothelial Growth Factor that induces neovascularization. Such neovascularization would mark the initiation of a set of determining mechanisms that translate pathways of cell proliferation to one of autonomous cell activity as constituted by the production of primary cellular receptor splice events.

Growth factor receptivity might evolve largely in terms of such splice events in the transcription of growth factors in a manner that induces persistent positive feedback pathways of cell stimulation.

The apparently contrasting influences of hypothalamic growth factor-, and of hormonal or releasing factor-, stimulation, and of primary pituitary cellular defects, might be resolved with regard to the creation of various truncated isoform or splicing alterations in growth factors involving interactive receptor participation.

Induced primary pituitary cell pathophysiology would paradoxically resolve as a hypothalamic ongoing stimulus for further change in anterior pituitary cell proliferation and subsequent adenoma formation.

Noncarcinomatous nature of pituitary neoplasms: A unified concept of pituitary tumorigenesis might implicate a coordinated system of potentiating suppressor gene suppression in the evolving transforming event[19]. It appears significant that pathways of adenomatous tumorigenesis are distinct from carcinogenesis of anterior pituitary cells. Pituitary adenomas might constitute a possible exit mechanism in neoplastic transformation that prevents malignant potentiality to evolve further. It is in terms of a series of multi-step mechanisms that pituitary adenomatous cell proliferation proves a consequence of possible negative or positive feedback effects of circulating hormones.

An interplay of effects involving possible hypothalamic drive that is interactive with feedback

influence might result in the institution of proliferation as predisposing circumstances in subsequent neoplastic transformation.

Such neoplastic transformation might be a realized pathway that is borne out as a consequence of driving influences that compound hypothalamic effect arising as possible feedback influence of circulating hormones. Pituitary tumors clonally expand as stimulated by hormones and growth factors/cytokines, especially estrogen and Beta-transforming growth factor[20].

Understanding the nature of various positive drives exerted by circulating hormones that feedback on anterior pituitary cells might help account for a relatively high incidence of pituitary adenomas of non-carcinomatous type. Somatic cell mutations possibly precede clonal expansion and play a major role in pituitary tumorigenesis[21].

An either/or phenomenon in development of pituitary adenoma or pituitary hyperplasia: Knockout and transgenic mouse models indicate a complex interplay of hormone insufficiency and of hormonal feed-forward positive influences in the development of pituitary tumorigenesis[22]. It appears that tumorigenesis complies with a series of contrasting negative and positive stimuli that suppress or accentuate the participation of genetic factors in pituitary cell proliferation. Pituitary Activin, a transforming growth factor-beta cytokine family member, regulates hormone biosynthesis and also cell growth and differentiation[23].

A central pathogenesis in development of pituitary adenomas would implicate the firm establishment of such proliferative activity as autonomously operative systems of increased hormone production. Human pituitary tumor transforming gene is involved early in pituitary tumorigenesis and in tumor progression by regulating production of basic fibroblast growth factor; this in turn activates angiogenesis and mutagenesis[9].

The variable phenotypic attributers of anterior pituitary cells that produce different hormones would correlate with the varied array of hypothalamic releasing hormones produced not only as modulators of pituitary hormone secretion but particularly as discriminating influences in the maintenance of different anterior pituitary cell subpopulations that are commonly active. It is in this sense that trophic cellular influences are intrinsically hormonally expressed in terms particularly of the development of hypothalamic responsiveness to excessive hormonal secretion. Understanding effects of excessive hormone levels as a paradoxical suppressive stimulus whereby hormones feed-forward development of hypothalamic function would underlie a complex interplay of responsive influences as hyperplasia of anterior pituitary cells in cases of primary peripheral endocrine gland insufficiency[24].

Cushing's syndrome would attest to a primary adrenal pathology that somehow feeds forward in the production and establishment of a pituitary adenoma in the apparent absence of hyperplasia of the pituitary as an integral organ. Methylation of p16 gene CpG island attests to molecular pathology in apparently normal pituitaries in patients with Cushing's disease[25].

Ultimately, perhaps, an organ-based adenoma is produced as a contrasting attribute of generalized hyperplasia of various anterior pituitary cell lines.

Anterior pituitary cell proliferation is distinct from adenomatous transformation: Inactivation of the p16 ink4a /p15 ink 4b/RB1 pathway appears an initiating mechanism in the development of proliferative activity of anterior pituitary cells. Hypermethylation of CpG islands inactivate transcription of these suppressor genes in a manner directly conducive to adenoma formation. This appears particularly relevant with regard to hormonally inactive glands as represented by pathways converging on proliferative stimulation of cells that evolve subsequently in a predetermined manner.

Stimulation of cell proliferation as a mechanism directly evolving as autonomous systems would necessarily convert the p16 ink4a/p15 ink4b/RB1 pathway to incorporate variable production in establishment of neovascularization. Autocrine and paracrine influences participate on an evolving endocrine background in the development of autonomous adenoma formation, apart from proliferative potential of the cells. As such, cell proliferation per se does not fully account for the emergence of an anterior pituitary adenoma that generally is unaccompanied by pituitary hyperplasia in most patients.

Nonfunctional pituitary adenomas appear to constitute a distinct type of cell proliferation that progresses largely along lines that do not involve paracrine, autocrine or endocrine systems of stimulation. The central concept of autonomous growth and proliferation of neoplastic cells contrasts with those of pituitary adenoma that are intimately related to excessive hormonal production and to hypothalamic secretagogue stimulation in many instances.

One might envisage a full panorama of effects[16] whereby development of secretory activity of pituitary adenomatous cells is a stimulus for persistent proliferation of the affected secretory cells in a manner akin to production of simple trophic factors in reparative systems.

One would recognize pituitary adenomas as

pathways of mechanistic stimulation that are related to hormonal secretory activity as the main stimulus for transformation of cells to a progressively autonomous behavior pattern. Resistance to say thyroid hormone may possibly predispose to pituitary hyperplasia and adenoma development[26].

Instances of pituitary hyperplasia arise mainly in a setting of failure of various primary endocrine organs such as the adrenal and thyroid. It would also appear that a contrasting series of system effects between pituitary hyperplasia and adenomatous proliferation is one derived from monoclonal attributes that arise initially as homotypic proliferation of a given characterized anterior pituitary cell subset[27].

In view of contrasting differences between a purely hyperplastic and a purely monoclonal pituitary adenomatous proliferation, there might evolve a series of combined effects that relate primarily to persistence of a characterized secretory activity of proliferating cells. There might indeed evolve a paradoxical situation whereby proliferation of cells in the first instance determines subsequent secretory patterns of the pituitary cells. Indeed, proliferation of such cells would affect hormonal secretion in a manner that would either accentuate further hormonal secretion or suppress it.

Nonfunctional anterior pituitary cells appear to represent an alternative pathway that often entails progressive growth and regrowth or recurrence of the adenoma after surgical treatment. One might recognize the emergence of pathways of substitution for secretory pathways that accentuate an initially instituted proliferative pattern of growth. In such a setting, cellular proliferation and cellular secretory activity would constitute primordial behavioral patterns that predetermine in many instances the subsequent nature and outcome of transformation events.

Natural evolution of anterior pituitary cell activity may be recognized as one often based on positive feedback control of cellular secretory activity.

It would perhaps be significant that nonsecretory or nonfunctional pituitary adenomas proliferate often to an increased extent in a manner that exceeds that of functional adenomas. A representation of a directly contrasting and conflicting system of proliferation versus secretion by anterior pituitary cells might account for the establishment of paracrine or autocrine pathways of semi-reparative mechanisms akin to keloid formation in the skin and to fibromatosis in soft tissues.

Hormonal and growth factor biology might simply constitute a centrally operative pathway that integrally incorporates a dual pathway of cytodifferentiation whereby cellular proliferation is one determining subsequent patterns of secretory activity in its own right. Furthermore, secretory cellular patterns are mechanisms tied up not only with stimulatory or trophic effects but especially with a divergence from essential autonomous patterns of cellular proliferation.

REFERENCES

1. Mohammed, HP., D.D. Seachrist,C.C. Quirk and J.H. Nelson, 2004. Reexpression of p8 contributes to tumorigenic properties of pituitary cells and appears in a subset of prolactinomas in transgenic mice that hypersecrete luteinizing hormone. Mol. Endocrinol., 18: 2583-93.
2. Clayton, R.N. and W.E. Farrell, 2001. Clonality of pituitary tumors: More complicated than initially envisaged? Brain Pathol., 11: 313-27.
3. Alexander, J.M., B.M. Biller, H. Bikkel, N.T. Zervas, A. Arnold and A. Klibanski, 1990. Clinically nonfunctioning pituitary tumors are monoclonal in origin. J. Clin. Invest., 86: 336-40.
4. Jacoby, L.B., E.T. Hedley-Whyte, K. Polaski, B.R. Seizinger and R.L. Martuza, 1990. Clonal origin of pituitary adenomas. J. Neurosurg., 73: 731-5.
5. Herman, V., J. Fagin, R. Gonsky, K. Kovacs and S. Melmed, 1990. Clonal origin of pituitary adenomas. J. Clin. Endocrinol. Metab., 71: 1427-33.
6. Schulte, H.M., E.H. Oldfield, B. Allolio, D.A. Katz, R.A. Berkman and I.U. Ali, 1991. Clonal composition of pituitary adenomas in patients with Cushing's disease: Determination by X-chromosome inactivation analysis. J. Clin. Endocrinol. Metab., 73: 1302-8.
7. Sauo, T., H. Horiguchi, B. Xu, C. Li, A. Hino, M. Sakeki, S. Kannuki and S. Yamada, 1999. Double pituitary adenomas: six surgical cases. Pituitary, 1: 243-50.
8. Spada, A., L. Valler and G. Faglia, 1993. "G-proteins and hormonal signalling in human pituitary tumors: Genetic mutations and functional alterations. Front Neuroendocrinol., 14: 214-32.
9. Faglia, G. and A. Spada, 2001. Genesis of pituitary adenomas: state of the art. J .Neurooncol., 54: 95-110.
10. Canneir, S., L. Curto, A. Lania, K. Saccomanno, FM. Salpietro and F. Trimarchi, 1999. Unusual MRI finding of multiple adenomas in the pituitary gland: A case report and review of the literature. Magn. Reson. Imaging, 17: 633-6.
11. Herman-Bouert, V. and J.A. Fagin, 1995. Molecular pathogenesis of pituitary tumors. Baillieres Clin, Endocrinol. Metab., 9: 203-23.

12. Yuand, R. and S. Melmed, 2001. Oncogene activation in pituitary tumors. Brain Pathol., 11: 328-341.
13. Farrell, W.E., A.P. Coll, R.N. Clayton, P.E .Harris, 2003. Corticotroph carcinoma presenting as a silent corticotrophic adenoma. Pituitary, 6: 41-7.
14. Larsen, J.B., H.D. Schroder, A.G. Sorensen, P. Bjarre and S. Heim, 1999. Simple numerical chromosome aberrations characterize pituitary adenomas. Cancer Genet. Cytogenet., 114: 144-9.
15. Alexander, J.M., B. Swearingen, G.T. Tindall and A. Klibamyki , 1995. Human pituitary adenomas express endogenous inhitin subunit and follistatin messenger ribonucleic acids. J. Clin. Endocrinol. Metab., 80: 47-52.
16. Ezzat, S., 2001. The role of hormones, growth factors and their receptors in pituitary tumorigenesis. Brain Pathol., 11: 356-70.
17. Zumkeller, W., 2003. The role of the GH/IGF system in pituitary tumorigenesis. Horm. Metab. Res., 35: 664-6.
18. Spada, A. and A. Lania, 2002. Growth factors and human pituitary adenomas. Mol. Cell Endocrinol., 197: 63-8.
19. Alexander, JM., 2001. Tumor suppressor loss in pituitary tumors. Brain Pathol., 11: 343-355.
20. Peez-Pereda, M., D. Giacomini, Dn. Refargo, A.C. Nageshima, U. Hofner, Y. Grubler and A. Cliervein *et al*, 2003. Involvement of bone morphogenetic protein 4 (BMP-4) in pituitary prolactinoma pathogenesis through a Smad/estrogen receptor crosstalk. Proc. Natl. Acad. Sci. USA., 100: 1034-9.
21. Herman, V., J. Fagin, R. Gonsky, K. Kovacs and S. Melmed, 1990. Clonal origin of pituitary adenomas. J. Clin. Endocrinol, Metab., 71: 1427-33.
22. Asa, S.L. 2001. Transgenic and knockout mouse models clarify pituitary development, function and disease Brain Pathol., 11: 370-383.
23. Danila, DC., X. Zhang, Y. Zhou, GR. Dichersim, JA. Fletcher, ET. Hedley-Whyte, and MK. Selig *et al*., 2000. A human pituitary tumor-derived folliculostellate cell line. J. Clin. Endocrinol. Metab., 85: 1180-7.
24. Schulte, HM., EH. Oldfield, B. Allolio, DA. Katz, RA. Berkman and IU. Ali, 1991. Clonal composition of pituitary adenomas in patients with Cushing's disease: Determination by X-chromosome inactivation analysis. J. Clin. Endocrinol.m. Metab., 73: 1302-8.
25. Simpson, DJ., AM. McNicol, D.C. Murray, A. Bahar, HE. Turner, JA. Wass and MM. Esiri *et al,* 2004. Molecular pathology shows p16 methylation in nonadenomatous pituitaries from patients with Cushing's disease. Clin. Cancer Res., 10: 1780-8.
26. Safer, J.D., S.D. Colan, L.M. Fraser and FE. Woudisford, 2001. A pituitary tumor in a patient with thyroid hormone resistance: A diagnostic dilemma. Thyroid., 11: 281-91.
27. Ma, W., H. Ikede, N. Weatabe, M. Kanno and T. Yoshimoto, 2003. A plurihormonal TSH-producing pituitary tumor of monoclonal origin in a patient with hypothyroidism. Horm. Res., 59: 257-61.