Neuro-endocrinology BRIEFINGS

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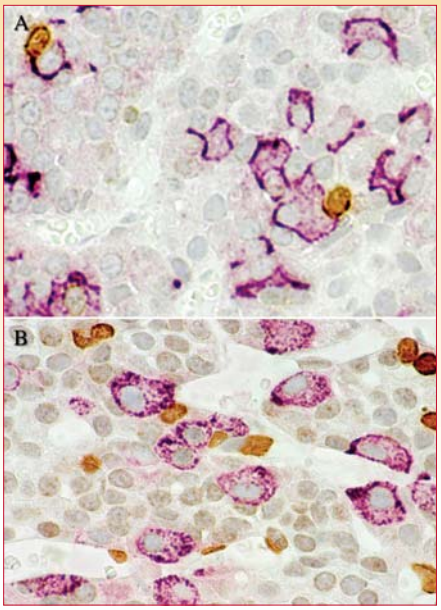
STEM CELLS, HORMONES AND PITUITARY ADENOMAS

SUMMARY

We still do not understand the pathogenesis of the majority of pituitary adenomas or why, once formed, their behaviour tends to be so benign. Understanding trophic activity in the normal pituitary may be the key. Despite the fact that changes in indices of cell division and programmed cell death that are too small to measure can produce highly significant fluxes in cell populations, little by little, the fascinating patterns of integrated responses of pituitary cells to hormonal stimuli are now being revealed.

Exuberant normality?

Pituitary tumours affect more than 10% of us by the time we die. Only a very small proportion come to clinical attention, usually as a result of hypopituitarism, compression of surrounding structures such as the optic chiasm, or excessive hormone secretion. Even when they do present, their behaviour tends to be remarkably benign with about 50% never growing beyond 1cm in diameter and the majority of larger ones either growing very slowly or not at all. A significant proportion of microprolactinomas resolve spontaneously, macroprolactinomas sometimes shrink to nothing and show no sign of returning even when long term dopamine agonist treatment is withdrawn, and some corticotroph adenomas have the bizarre propensity to cycle repeatedly through periods of normal and abnormal hormone secretion. Many pituitary adenomas remain responsive to physiological hormonal signals and metastatic spread is exceptionally rare. The quest to implicate classical oncogenes and tumour suppressors in pituitary adenoma formation has been almost entirely unsuccessful and although many pituitary tumours are believed to be aneuploid and clonally skewed - both characteristics of 'true tumours' – the malignant credentials of these lesions are, all in all, pretty unconvincing.



Double immunohistochemistry for BrdU (a marker of cell cycle activity) and ACTH (panel A) or luteinizing hormone (panel B), in the anterior pituitary of rats that have been both adrenalectomized and gonadectomized four days previously (ie. at the height of the mitotic response). Hormone- and BrdU-positive cells are abundant, but cells expressing both are few and far between (none shown).

Figure courtesy of Lesley A Nolan.

Most researchers in the field are now persuaded that hypothalamic dysfunction is rarely involved in the induction of pituitary adenomas, but the possibility that the hormonal microenvironment has a highly significant effect on pituitary adenoma behaviour and propagation once they are formed is again becoming harder to dismiss. As many of the characteristics of pituitary adenomas emulate 'exuberant normality' rather than benign malignancy, the control of mitosis and apoptosis in the normal pituitary in response to hormonal signals has again come under close scrutiny.

So how does the normal pituitary control the relative populations of different cell types that it contains? For many years it was believed that under constant conditions nothing much happened trophically in the adult pituitary at all. The assumption was that a hormonal stimulus such

as bilateral adrenalectomy would induce corticotroph cell division to keep abreast of increased adrenocorticotrophic hormone (ACTH) secretory requirements via the trophic effects of increased corticotrophin releasing hormone (CRH) from the hypothalamus. And even when all of the various factors that confound quantitative immunocytochemistry are taken into account, dramatic changes in relative cell populations do indeed occur. Not only that, but if you look hard enough for long enough, it's possible to catch occasional ACTH-positive cells in the process of division. Furthermore, if you infuse high enough doses of CRH for long enough, pituitary cell division can be shown to increase. The problem with these observations is that the number of hormonally identifiable cells that divide is far too small to account for the rapidity of population changes seen. The story of what's actually happening is far from complete but is now gradually being pieced together.

Oligopotent cells

One to two percent of cells in the pituitary are active oligopotent stem cells that continue to undergo mitotic activity at a fairly steady rate that gradually decreases with age. Turnover is also subject to subtle diurnal variation and is temporarily inhibited by pharmacological levels of glucocorticoids. Basal pituitary mitotic rate attributable to this active oligopotent stem cell pool, unassuming though it seems, is sufficient to generate enough new cells to entirely replace the pituitary every 5 weeks or so if they all survived. Of course, in the absence of any changes in environmental, physiological or psychological stress, most of them don't. The few that do escape early

"... the limited mitotic activity of the daughter cells of oligopotent stem cells is tonically inhibited ..."

apoptosis persist as hormone receptor-expressing but hormonally null progenitor cells that are able to undergo several rounds of cell division if, and only if, endocrine circumstances change. And it is sudden changes rather than persistent hormonal abnormalities that seem to be the key to the induction of trophic activity.

It turns out that the limited mitotic activity of the daughter cells of oligopotent stem cells is tonically inhibited by corticosterone and testosterone, and stimulated by estrogen and thyroid hormones. A sudden reduction in corticosterone, for example, induces a self-limiting wave of increased mitosis, giving rise to hormonally null daughter cells. Exactly the same happens after orchidectomy. Withdrawal of both corticosterone and testosterone together produces a wave of increased mitotic activity that is no bigger than either alone. So it's very likely to be one and the same population of cells that respond to both stimuli. But if all of this frenetic but self-limiting mitotic activity gives rise to hormonally null cells, how is it that the number of hormonally positive cells rapidly changes? It's certainly not the newly formed cells differentiating. Instead, it turns out that pre-existing hormonally null cells, formed at least 2 to 3 weeks previously are independently stimulated by the same hormonal changes and simultaneously differentiate into hormone-secreting subtypes. Far from accounting for the lion's share of new cells, division of pre-existing hormonally-defined cells accounts for less than 5% of the increase following hormonal changes.

However, the most dramatic physiological changes in pituitary structure and function occur during pregnancy and although it seems a straightforward question to sort out, it is still not certain how the striking changes in relative proportions of prolactin- and growth hormone-producing cells during pregnancy are brought about or how they largely resolve after weaning. Neither is it clear whether in addition to acute changes, continuous estrogen exposure can exert a more subtle but persistent effect over weeks and months. Taking all of the data together, there's a suspicion that specific co-regulatory systems linking the discrete molecular machinery of mitosis with that of apoptosis might be implicated in pituitary tumour induction and that the epiphany in our understanding of pituitary adenomas has yet to come.

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