Stress-Response Proteins in Human Pituitary Adenomas

Expression of Heat-Shock Protein 72 (HSP-72)

George Kontogeorgos, Lucia Stefaneanu, and Kalman Kovacs

Department of Pathology, General Hospital of Athens, Greece; Department of Pathology, St. Michael’s Hospital, University of Toronto, Ontario, Canada

The presence of heat-shock protein 72 (HSP-72) was investigated by immunohistochemistry (IHC) in a series of 28 surgically removed pituitary adenomas including six somatotroph, two mammosomatotroph, five lactotroph, six corticotroph, four null cell adenomas, and three oncocytomas. Overall, 25 tumors (90%) were positive for HSP-72. One somatotroph, one lactotroph, and one null cell adenomas each contained only sparse, small HSP-72 immunoreactive granules and were regarded as negative. The expression of HSP-72 was commonly uneven differing in degree from cell to cell and among various tumors. In most adenomas, the immunoreactivity was seen as fine granules of moderate density, distributed throughout the cytoplasm. In some cells, the immunoreactivity was strong and diffuse. In one somatotroph, two corticotroph, one null cell, and one oncocytic adenomas, nearly all tumor cells were strongly positive. Adenoma cells, located adjacent to capillaries and small vessels, commonly showed a selective and strong immunoreactivity for HSP-72. The fragments of nontumorous adenohypophysial parenchyma also contained fine immunoreactive cytoplasmic granules accumulating in scattered hormone-producing cells and in stellate cells. These results show that HSP-72 is expressed in most pituitary adenomas with a mostly focal and less frequently diffuse pattern of overexpression.

Key Words: Heat-shock proteins (HSPs); histology; immunohistochemistry (IHC); microwaves; pituitary adenoma; stellate cells.

Introduction

Stress-response proteins (SRPs), also known as heat-shock proteins (HSPs), are produced in response to a non-lethal thermal shock or other stressful conditions, in order to resist sudden changes and to repair cell damages (1,2). The role of SRPs in normal cells is connected with protein assembly and disassembly (3), proliferation (4), and differentiation (1), as well as with signal transduction mechanisms (5). In addition, SRPs have been found to interact with c-myc, H-ras, and p53 oncoproteins in lung tumors, and normal and pathological thyroid tissues in humans (6-8). However, their role in neoplastic lesions remains obscure.

With regard to endocrine function, SRPs are thought to be implicated in regulation of the functional activities of various endocrine glands and target tissues. By binding to steroid receptors, they maintain the receptor stability and mediate the receptor–DNA interactions (9-11). Their functional activities in various endocrine- and hormone-dependent tissues were recently reviewed (12).

The study of SRPs in pituitary adenomas and nontumorous pituitaries is limited. HSP-25 has been localized by immunohistochemistry (IHC) in several cells of the rat adenohypophysis, corresponding to gonadotrophs or thyrotrophs (13). In two separate studies of human brain tumors including pituitary adenomas, HSP-72 was demonstrated by IHC in one of eight tumors, whereas two of five adenomas were immunopositive for HSP-27 (14,15). In addition, 2 of 10 noninvasive and 5 of 10 invasive pituitary adenomas were found to express HSP-27 (16). Lastly, ubiquitin, a nonlysosomal protein involved in chromatin structure and degradation, was localized in 43.5% of pituitary adenomas and in Crooke’s cells in 83% of glucocorticoid-treated patients (17).

In the present study the expression of HSP-72 by IHC in a representative series of all common categories of pituitary adenomas was investigated, in order to identify the particular adenoma types that show immunoreactivity and to document sites of overexpression.

Results

Overall, approx 90% (25 of 28) of adenomas were immunopositive for HSP-72. One somatotroph, one lactotroph, and one null cell adenomas containing only sparse faint immunopositive granules with no evidence of over-
expression were regarded as immunonegative for HSP-72. The degree and intensity of immunoreactivity were uneven, differing from cell to cell in the same tumor and among various adenomas. Dispersed fine granules of moderate density, diffusely distributed throughout the cytoplasm, represented a common pattern of immunoreactivity. Some adenoma cells, scattered or focally arranged in groups, exhibited strong and diffuse immunopositivity (Figs. 1 and 2). In 5 of 28 adenomas (one somatotroph, two corticotrophs, one null cell, and one oncocytoma), nearly all cells were strongly immunopositive. Selective and strong immunopositivity was commonly noted in adenoma cells adjacent to capillaries and small vessels (Fig. 3). Even in adenomas exhibiting strong and diffuse HSP-72 immunopositivity, the cells adjacent to capillaries were more prominently immunoreactive. In addition, several, scattered hormone-producing cells were encountered within fragments of nontumorous adenohypophysial containing various amounts of immunoreactive cytoplasmic granules (Fig. 4), which were also accumulated in S-100 protein immunopositive stellate cells forming follicles (Fig. 5). The latter exhibited characteristic dot-like, paranuclear pattern of immunoreactivity, probably corresponding to the prominent Golgi apparatus. Paranuclear localization of HSP-72 was also encountered in scattered stellate cells in one corticotroph adenoma (Fig. 6).