

This Week's Citation Classic®

Tashjian A H, Yasumura Y, Levine L, Sato G H & Parker M L. Establishment of clonal strains of rat pituitary tumor cells that secrete growth hormone. *Endocrinology* 82:342-52, 1968; and **Tashjian A H, Barowsky N J & Jensen D K.** Thyrotropin releasing hormone: direct evidence for stimulation of prolactin production by pituitary cells in culture. *Biochem. Biophys. Res. Commun.* 43:516-23, 1971.
[Depts. Pharmacol., Harvard Sch. Dental Med. and Harvard Med. Sch., Boston; Grad. Dept. Biochem., Brandeis Univ., Waltham, MA; and Dept. Med., Washington Univ., St. Louis, MO]

The first paper describes the methods for establishing and characterizing growth hormone-producing clonal cell strains from a functional, transplantable rat pituitary tumor. Subsequently, two of these strains were shown to synthesize and secrete prolactin. The second paper describes the surprising discovery that the first-characterized hypothalamic neuropeptide, thyrotropin-releasing hormone, acted not only on thyrotropic cells but also on lactotrophs. [The *SCI*® indicates that these papers have been cited in more than 460 and 475 publications, respectively.]

Hormone-Producing Cell Culture Models

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In the early 1960s, I decided to leave clinical medicine for a career in the laboratory as an endocrine cell biologist. My postdoctoral mentor at Harvard, Paul Munson, encouraged me to learn immunology with L. Levine and cell biology with G.H. Sato, both at Brandeis University. Studies on the immunochemical specificity of primate growth hormones (GH) with Levine, and the lack of human GH for clinical usage, led Y. Yasumura, Sato, and me to try to establish human GH-producing cells in continuous culture.

Because of slow progress, we turned to functional animal tumor cells as a model system using the novel enrichment culture techniques pioneered in the Sato lab.¹ These methods were successful and focused initially on GH-producing rat pituitary tumors, and several novel clonal cell strains were established as described in the first paper. Several clones produced prolactin (PRL) as well as GH.²

Because GH₃ cells had a high constitutive rate of PRL secretion, I reasoned that they could be used as a bioassay to identify the then-known, but unidentified, hypothalamic PRL-inhibiting

factor. To my surprise, the first experiments revealed that hypothalamic extracts did not inhibit PRL secretion by GH₃ cells but markedly enhanced its production. This unexpected observation quickly led to the even more unanticipated discovery that the active component in the extracts was thyrotropin-releasing hormone (TRH) (the 1971 paper). This was a surprising result because it was then generally considered that each hypothalamic regulatory peptide was selective and specific for stimulation or inhibition of a single cell type in the anterior pituitary gland.

The frequent citation of these two papers reflects the subsequent wide use of these stable functional cell strains for the isolation of the GH gene, for molecular studies on the regulation of GH and PRL gene expression,³ for extensive electrophysiological studies as a paradigm for electrically excitable nonneuronal secretory cells,⁴ for biochemical studies on the receptors and transduction mechanisms for vasoactive intestinal peptide (a potent PRL-releasing factor), somatostatin (the global secretion inhibitor), bombesin, and TRH. Indeed, the TRH receptor in these cells has proven to be prototypic of the class of membrane receptors that transduces an extracellular hormonal message via the intracellular signals of inositol polyphosphates, cytoplasmic Ca²⁺, and protein kinase activation.^{5,6}

Some investigators object to the use of neoplastic cells in culture as models for normal physiological events, but the universal availability of these cells to cell biologists, molecular biologists, neuroscientists, and endocrinologists worldwide, and an extensive list of normal physiological processes and mechanisms either discovered or elucidated in these cells, validate their utility as a highly informative model system.

For contributions to neuroendocrinology, peptide hormone action, and regulation of calcium metabolism, in 1977 I received the Harry B. Van Dyke Memorial Award and Lectureship from Columbia University and the Edwin B. Astwood Lectureship and Award from The Endocrine Society.

1. Yasumura Y, Tashjian A H & Sato G H. Establishment of four functional, clonal strains of animal cells in culture. *Science* 154:1186-9, 1966. (Cited 160 times.)
2. Tashjian A H, Bancroft F C & Levine L. Production of both prolactin and growth hormone by clonal strains of rat pituitary tumor cells. Differential effects of hydrocortisone and tissue extracts. *J. Cell Biol.* 47:61-70, 1970. (Cited 310 times.)
3. Samuels H H, Forman B M, Horowitz Z D & Ye Z-S. Regulation of gene expression by thyroid hormone. *J. Clin. Invest.* 81:957-67, 1988.
4. Ozawa S & Sand O. Electrophysiology of excitable endocrine cells. *Physiol. Rev.* 66:887-952, 1986.
5. Drummond A H. Inositol lipid metabolism and signal transduction in clonal pituitary cells. *J. Exp. Biol.* 124:337-58, 1986.
6. Gershengorn M C. Mechanism of thyrotropin releasing hormone stimulation of pituitary hormone secretion. *Annu. Rev. Physiol.* 48:515-26, 1986.

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