16. ANIMAL MODELS OF THYROID CARCINOGENESIS

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INTRODUCTION

Thyroid nodules affect approximately 20% to 45% of the population during their lifetime, but only a minority of nodular goiters bear a clinically relevant malignant potential. A simple diagnostic approach solving this problem does not exist. Cytological evaluation after fine needle aspiration obtained from thyroid nodules allows only for the detection of thyroid carcinoma in 80% to 90% of the cases. Thus, better methods predicting the malignant potential of thyroid nodules and/or diagnosing existing malignancies are urgently needed. To solve this problem the first step was designating animal models of thyroid carcinogenesis that help to understand this process in more detail. Last century's investigations in this field showed that the thyroid gland serves as a useful experimental model for understanding tumor formation not only in endocrine systems but, in epithelial tissues in general. Since the mid-1930s, the study of experimental carcinogenesis in rats, mice, hamsters, guinea pigs, sheep and swine has been focus of attention. In vivo, the growth of the follicular epithelium is controlled by a single tropic stimulus, the thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary gland at a rate dependent on the serum concentration of thyroid hormones (T3 and T4). Inhibition of this feedback loop by reduction or abolition of T3/T4 production leads to an increase in serum TSH. This initially induces an uniform hyperplasia of thyroid follicular epithelium, the first step of tumorigenesis. The discovery of the thyrostatic effect of some naturally occurring substances and the subsequent development of numerous synthetic preparations with the same action

gave an impetus to and provided an opportunity for the systematic investigation of morphological and functional changes in thyroids of experimental animals.

HISTORICAL OVERVIEW

In 1909, McCoy was the first to systematically investigate thyroids of animals. He searched for tumors in 23,000 wild rats, but failed to detect them. Eight years later, Bullock and Rhodenburg identified nine tumors in 4,300 rats. In 1926, Slye at al found 12 so-called carcinomas in 51,700 mice. All these tumors were spontaneous tumors. After the description of goiter in man (Marine 1924), the era of experiments in the field of thyroid carcinogenesis started sporadically with the investigations of Wegelin (1928), Hellwig (1935), and Hercus & Purves (1936). In the following time, each decade was influenced by leading research groups. In the 1940s, Purves, Bielschowsky, Kennedy and Griesbach (New Zealand, Germany) described the role of low iodine intake and continued the investigation of other positive goitrogenic agents. Kennedy, therefore, synthesized a quantity of allylthiocyanate (mustard oil), from a glucoside in mustard seeds, which were also goitrogenic. This compound was too toxic to be fed to rats, but when treated with ammonia, it was converted to allylthiourea and could be incorporated in the rat diet. It was shown that such drugs are goitrogenic, as is a deficiency of iodine, because they block the production of thyroid hormone. In the 1950s-1970s, Lindsay, Chaikoff (USA) and Doniach (U.K.) described the effects of external and internal irradiation on thyroid tumor production and gave evidence of a dose-dependent relationship. In the 1980s, Hesch, von zur Mühlen (Germany) and Dumont (Belgium) searched for tumor-initiating mechanisms through hormone dysbalances (TSH vs. TRH) and detected morphological changes by electron microscopy. Williams and Wynford-Thomas (U.K.) clarified the functional role of TSH and described differential gene expression (*ras*) in experimental thyroid tumors for the first time (Lemoine et al 1988). In the 1990s, Brabant, Dralle and Hoang-Vu (Germany) conducting short-term and long-term studies, investigated the regulatory mechanisms of thyroid tumorigenesis and described the changes of histology, ultrastructure, function, and proliferation in detail. In the present time, experiments performed by Japanese and Russian groups (Hirose, Hoshi, Hiasa, Nadolnik) focus on testing the carcinogenic potential of several parts of nutrition and diverse environmental factors.

THE PROBLEM OF TUMOR CLASSIFICATION

All the difficulties encountered in the classification of human thyroid tumors have to be faced in an attempt to classify thyroid tumors in animals, particularly in the rat. In early experiments, the well-known absence of clear-cut histological criteria for distinguishing reactive hyperplasia from neoplasia or benign from malignant tumorous growth has been reflected in publications describing corresponding lesions in the rat. In most cases, the authors have tried to apply the nomenclature of human pathology to the lesions observed in the rat thyroid. This approach has not only some easily recognizable advantages, but also some disadvantages. On the one hand, the use of similar terms would provide an opportunity for conducting a comparative analysis of