Praomys (Mastomys) natalensis:
A Model for Gastric Carcinoid Formation

OLA NILSSON, M.D., Ph.D., BO WÄNGBERG, M.D., LENA JOHANSSON, IRVIN M. MODLIN, M.D. Ph.D., AND HÅKAN AHLMAN, M.D., Ph.D.

Department of Histology, University of Göteborg, Department of Surgery, Sahlgrenska Hospital, Göteborg, Sweden, and Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

The gastric carcinoid tumors of *Praomys (Mastomys) natalensis* have been reviewed with respect to histogenesis, development, biochemistry, and morphological properties. Multi-centric gastric carcinoids frequently develop in the oxyntic mucosa of aging *Mastomys*. The development of these tumors can be significantly enhanced by drug-induced hypergastrinemia, e.g., histamine₂-receptor blockade. Spontaneous and drug-induced gastric carcinoids are endocrine in nature, as evidenced by their argyrophilic staining properties and chromogranin A content. They are also rich in histidine decarboxylase activity and produce large amounts of histamine, although other hormones, such as peptide YY and enteroglucagon, have also been demonstrated in these tumors. Ultrastructurally, gastric carcinoids are composed of tumor cells with typical secretory granules resembling those of enterochromaffin-like (ECL) cells. A close examination of the gastric carcinoids in *Mastomys* reveals striking similarities with gastric carcinoids developing in humans suffering from chronic atrophic gastritis type A or from the Zollinger-Ellison syndrome in combination with multiple endocrine neoplasia type 1 (MEN-1). Both these conditions are associated with hypergastrinemia and a higher risk for developing multi-centric gastric carcinoids of ECL-cell origin. The *Mastomys* tumor model therefore appears to be a significant experimental model in which induction and formation of gastric carcinoid tumors can be studied.

INTRODUCTION

The diagnosis and management of gastric carcinoid tumors has been the subject of much debate over the years [1–10]. Gastric carcinoids in man may occur sporadically, but they frequently arise in patients with chronic atrophic gastritis of the non-antral mucosa (CAG type A) [11–13]. Patients with the Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1 (MEN-1) also have a greater risk of developing gastric carcinoids [14]. A common feature in these two groups of patients is prolonged hypergastrinemia. It has therefore been suggested that achlorhydria or excessive production of gastrin from a gastrinoma will cause hypergastrinemia,

leading to hyperplasia of the gastric enterochromaffin-like (ECL) cells and to formation of gastric carcinoids [15–17]. Although vigorously challenged [18,19], this hypothesis has prompted experimental studies to elucidate the mechanisms regulating ECL-cell growth. A powerful tool in ECL-cell research became available with the introduction of potent inhibitors of gastric acid secretion, i.e., histamine$_2$-receptor blockers and proton pump inhibitors. These drugs induce sustained hypergastrinemia and cause proliferation of gastric ECL cells, which, after lifelong treatment of experimental animals, may transform into gastric carcinoids [20–22].

Experimental studies on gastric ECL-cell growth and carcinoid formation have been performed primarily in rodents. The earliest studies utilized the African rodent *Praomys (Mastomys) natalensis*, which is prone to develop spontaneous gastric carcinoids in the oxyntic mucosa [23]. Later studies on ECL-cell growth were carried out in rats and mice, where gastric carcinoids developed after lifelong treatment with potent inhibitors of acid secretion [20–22]. In recent years, the interest in gastric carcinoids of *Mastomys* has been renewed because it was shown that carcinoid tumors develop very rapidly in this species during histamine$_2$-receptor blockade [24]. This review will focus on the biology of the *Mastomys* gastric carcinoids and discuss the relevance of this tumor model in relation to the human situation.

HISTORICAL ASPECTS

Praomys (Mastomys) natalensis or "the multimammate mouse" is one of the most common wild rodents in Africa and plays an important role in the natural cycle of several zoonoses [25]. It has been widely used in laboratories as a vector for diseases such as plague, Lassa fever, and bilharzia; however, a high incidence of gastric tumors was noted in a laboratory strain of *Mastomys* in the late 1950s [26]. Gastric tumors and mucosal hypertrophy were observed in 40 percent of *Mastomys* dying from natural causes. These gastric tumors were initially characterized as adenocarcinomas but were later shown to possess endocrine features and were thus reclassified as gastric carcinoids [23]. In addition to gastric carcinoids, *Mastomys* may also develop tumors in various other organs, including liver, spleen, thymus, pituitary, and adrenals [27]. The incidence of gastric carcinoids increases with age and has been reported to be as high as 40–60 percent in *Mastomys* 12–24 months of age [27,28]. The malignant potential of gastric carcinoids was soon recognized, as well as the capacity of these tumors to grow after transplantation to other *Mastomys* or to nude mice [23,29–33]. Transplantation of carcinoid tumors for several generations has generated different substrains of tumors with distinct differences in hormone production [31–33]. Inbreeding of *Mastomys* has created two different strains, designated Y and Z. The Z strain develops spontaneous antral adenocarcinomas and fundic carcinoids, while the Y strain, like the wild type, develops only fundic carcinoids [34–36]. Subsequent studies in *Mastomys* have been focused either on gastric carcinoids or on gastric adenocarcinomas [36,37]. The following sections will examine the gastric carcinoid tumors in *Mastomys* and describe some important characteristics of these tumors.

CARCINOID TUMOR IN *MASTOMYS*

Hormone Production

Gastric carcinoids in *Mastomys* secrete a variety of amine and peptide hormones. Histamine, as well as the histamine-synthesizing enzyme histidine decarboxylase

(HDC), can be demonstrated in tumor extracts [31,38–41]. Tumor-bearing animals have elevated levels of histamine in peripheral blood and an increased urinary excretion of histamine [30,31]. Excessive production of histamine from gastric carcinoids may induce acid hypersecretion and cause severe gastric or duodenal ulceration in tumor-bearing animals [29]. There is also evidence that some gastric carcinoids, and subtypes thereof, may produce serotonin. The A- and E-lines of transplantable gastric carcinoids described by Hosoda et al. [30–33] contain significant amounts of serotonin and tryptophan hydroxylase, the enzyme converting tryptophan to the serotonin precursor, 5-hydroxytryptophan. Blood levels of serotonin as well as urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) are also elevated in animals transplanted with the A- or E-line tumors. Tumor-bearing animals may also show typical carcinoid vasoreactions upon provocation with volatile anesthetics [32].

Assay of peptide hormones has demonstrated large amounts of peptide YY (PYY) and enteroglucagon (EG) in gastric carcinoid tumors of hypergastrinemic *Mastomys* [24,42]. Plasma levels of PYY and EG were also consistently elevated in tumor-bearing animals. Other peptide hormones, i.e., gastrin, somatostatin, bombesin, VIP, pancreatic polypeptide, gastric inhibitory polypeptide, secretin, and CCK-8 were not detectable in tumor extracts.

Morphological Characteristics

Gastric carcinoids in *Mastomys* are located in the acid-producing (oxyntic) part of the gastric mucosa. Gross lesions appear as multiple elevated nodules, frequently with a central ulceration, and a major submucosal tumor mass [28]. In the early *Mastomys* colonies, carcinoid tumors were shown to have a malignant potential with metastatic growth in regional lymph nodes and liver in approximately one-fourth of the tumor-bearing animals [23,28]. Microscopic examination of gross tumors revealed submucous nodules with neoplastic cells in trabecular or adenoid patterns. The surrounding gastric mucosa was usually hyperplastic. Intramucosal carcinoids (microcarcinoids), however, were frequently observed in macroscopically normal mucosa. The endocrine nature of tumors was demonstrated by the argyrophil reactions of Sevier-Munger or Grimelius [23,28,29,40,41,43]. Hyperplastic lesions usually had a strong argyrophilia, while dysplastic and neoplastic lesions displayed a weaker argyrophil reaction. The tumor cells belonged to the APUD family of endocrine cells [44], since they had the capacity to take up and decarboxylate amine precursors [40]. Immunocytochemical studies demonstrated chromogranin A in a majority of tumor cells, confirming the endocrine nature of the tumors [41]. A majority of tumor cells was labeled by antisera against histamine, while no labeling was obtained with antisera against gastrin, somatostatin, serotonin, or bombesin [41,45]. A minor population of tumor cells in hypergastrinemic *Mastomys* was labeled by PYY and enteroglucagon antisera [43,46], indicating biochemical heterogeneity of tumor cells. Ultrastructural analysis of carcinoid tumors confirmed the endocrine nature of these tumors and demonstrated specific secretory granules in tumor cells [24,28,40,46,47]. The number of granules in each tumor cell was usually lower than that observed in normal gastric endocrine cells, and some tumor cells even lacked secretory granules. The tumor cell granules were characterized by an electron-dense core surrounded by a limiting membrane. A variety of structurally distinct secretory granules have been described, which may reflect biochemical or functional differ-
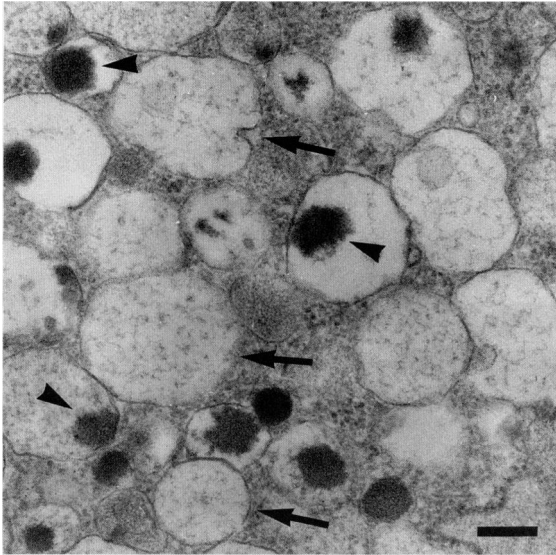
FIG. 1. Ultrastructure of typical proliferating gastric endocrine cell in hypergastrinemic *Mastomys* (loxtidine-treated). Most secretory granules are of the vesicular type with a limiting membrane and electron-lucent content (*arrows*). Some secretory granules contain a small electron-dense core which is eccentrically located (*arrowheads*). The appearance of the secretory granules is very similar to that observed in normal gastric ECL cells. Electron microscopy. Uranyl and lead. Bar indicates 200 nm.

ences among tumor cells. In hypergastrinemic *Mastomys,* tumor cell granules were commonly of the vesicular type, similar to those observed in normal gastric ECL cells [48] (Fig. 1).

Histogenesis of Tumors

The morphological changes occurring in the gastric mucosa of *Mastomys* prior to the formation of spontaneous carcinoids have been examined by Soga et al. [43]. They have classified the proliferative changes in the endocrine cell population of the fundic mucosa into three stages. During stage I (hyperplastic), proliferation of endocrine cells takes place within the basal part of the gastric glands and comprises an increased number of endocrine cells, occasionally forming chains. During stage II (pre-neoplastic), endocrine cells form larger nodules, which are still contained within the gastric glands. During stage III (neoplastic), endocrine cells grow outside the glands in the lamina propria and eventually form larger masses (micro- and macrocarcinoids). These changes are multi-focal and occur in all parts of the fundic mucosa. No changes are observed among the endocrine cells of the antral mucosa [43].

The speed by which gastric endocrine lesions develop in *Mastomys* can be greatly enhanced by histamine$_2$-receptor blockade [24]. This fact has facilitated the detailed analysis of gastric carcinoid formation in this species. The sequential development of hyperplastic, dysplastic, and neoplastic ECL-cell lesions during insurmountable histamine$_2$-receptor blockade by loxtidine have been described [41]. The histopathological classification system described by Solcia et al. [49] for gastric non-antral endocrine growths was used in these studies. Although this classification system was originally developed to describe endocrine cell lesions in the oxyntic mucosa of man, it has proved to be useful and accurate when describing endocrine cell proliferation in the oxyntic mucosa of *Mastomys*. Loxtidine treatment for eight weeks caused a marked hyperplasia of ECL cell. The hyperplasia was "diffuse" (simple) and
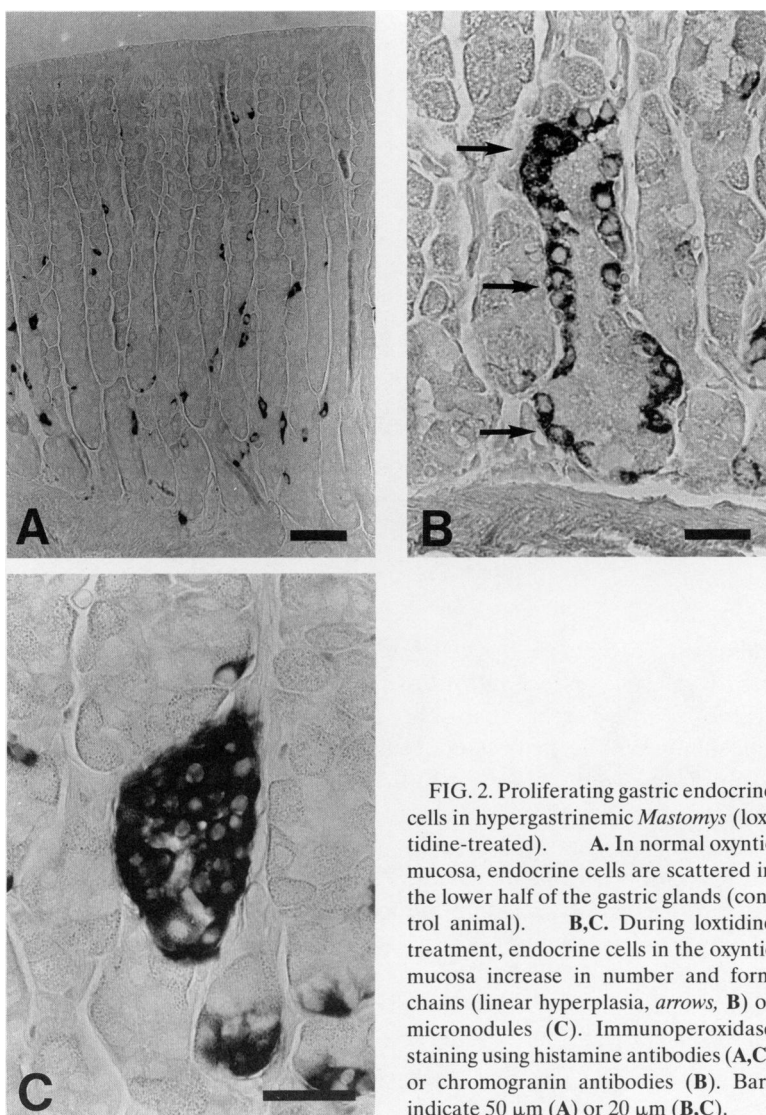
FIG. 2. Proliferating gastric endocrine cells in hypergastrinemic *Mastomys* (loxtidine-treated). **A.** In normal oxyntic mucosa, endocrine cells are scattered in the lower half of the gastric glands (control animal). **B,C.** During loxtidine treatment, endocrine cells in the oxyntic mucosa increase in number and form chains (linear hyperplasia, *arrows,* **B**) or micronodules (**C**). Immunoperoxidase staining using histamine antibodies (**A,C**) or chromogranin antibodies (**B**). Bars indicate 50 μm (**A**) or 20 μm (**B,C**).

characterized by an increase in the ECL-cell density (100 percent above normal controls), while typical linear or nodular hyperplasia was rare. After 16 weeks of treatment, there was a marked ECL-cell hyperplasia, which was characterized by the formation of numerous chains and micronodules of endocrine cells (Fig. 2). At this point, dysplastic lesions, e.g., microinvasive growth or enlarging micronodules, appeared in some animals. Extensive growth of dysplastic lesions of endocrine cells was observed after 24 and 32 weeks of treatment, particularly in the basal part of the gastric mucosa. Micro- and macrocarcinoids were also present in one-fourth to one-third of the animals at this point (Fig. 3). Histamine concentrations and HDC activity in the fundic mucosa increased gradually during histamine$_2$-receptor block-
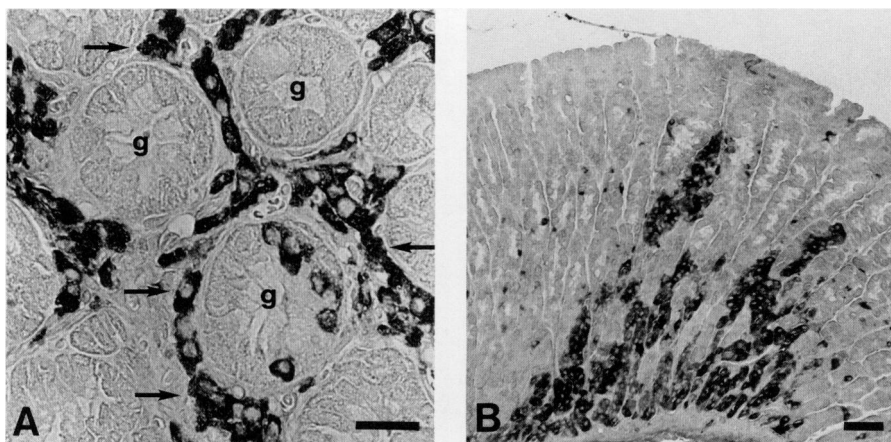
FIG. 3. Proliferating gastric endocrine cells in hypergastrinemic *Mastomys* (loxtidine-treated).   **A.** Endocrine cells are growing outside the gastric epithelium (microinvasive growth) (*arrows*).   **B.** Fusing micronodules are forming a microcarcinoid. Immunoperoxidase staining using chromogranin antibodies. Bars indicate 20 μm.

ade in parallel with the endocrine cell proliferation. The gradual accumulation of hyperplastic, dysplastic, and neoplastic changes over time suggests that carcinoid tumors develop from hyperplastic and dysplastic lesions [41]. Similar, although less pronounced, changes in the gastric endocrine cell population of *Mastomys* have been observed after proton pump inhibition [50].

The factors responsible for the development of gastric carcinoids in *Mastomys* are poorly understood. The genetic defects in *Mastomys* that make this species suscepti- ble to tumor development are unknown. The rapid induction of gastric carcinoids during histamine$_2$-receptor blockade-induced hypergastrinemia suggest, however, that gastrin may act as a promoter of tumor growth. This assumption is supported by the fact that gastrin/CCK receptors are abundant on tumor cell membranes from *Mastomys* gastric carcinoids [51,52]; however, the mechanisms regulating ECL-cell growth have primarily been studied in other species, e.g., in the rat. In this species, hypergastrinemia induced pharmacologically by inhibition of acid secretion, surgi- cally by partial corpectomy, or by direct infusion of gastrin stimulates the self- replication rate of ECL cells [53–57]. This process leads to an increased mucosal thickness and ECL-cell density. In the rat, these changes are reversible after short-term (ten weeks) hypergastrinemia [53]; however, life-long (>1.5 years) inhibition of acid secretion or partial corpectomy in rats eventually leads to forma- tion of gastric carcinoids [20–22,55]. From these studies, it is evident that gastrin plays an important role in the generation of ECL-cell tumors, although the exact role of gastrin in the transformation of ECL cells remains to be elucidated. It is possible that gastrin stimulates ECL-cell proliferation directly by activating gastrin/CCK receptors on the ECL cell, but it may also be that gastrin exerts its trophic action indirectly by stimulating local production of growth factors, e.g., epidermal growth factor or transforming growth factor alpha.

Hypergastrinemia induced by acid inhibition also produces changes in the antral endocrine cell population of the rat. The number of antral G cells increases during

omeprazole treatment, while the number of D cells decreases. The result is a marked increase in the G/D cell ratio in the antral mucosa [58]. Somatostatin receptor expression is abundant in the gastrointestinal tract as well as in gut neuroendocrine tumors [52,59,60]. The decrease in antral D cells and somatostatin contents observed during omeprazole treatment may therefore imply a downregulation of mechanisms inhibitory for ECL-cell growth. The proliferation of ECL cells may therefore be the consequence of an imbalance between factors stimulating growth and factors inhibiting ECL-cell growth. Our knowledge about these factors is still limited and will be the focus of future research.

Relevance of the Mastomys *Tumor Model*

The relevance of the *Mastomys* tumor model to human gastric carcinoids is dependent on the extent to which the *Mastomys* gastric carcinoids share the biological properties of their human counterparts. Gastric carcinoids in man can be divided into two groups: *(1)* multiple small tumors (predominantly composed of ECL cells) associated with hypergastrinemia and chronic atrophic gastritis (CAG) type A or Zollinger-Ellison syndrome and MEN-1 [12,61,62] and *(2)* solitary tumors occurring sporadically and not associated with hypergastrinemia. The solitary gastric carcinoids within the fundus corpus were first believed to be rare (3 percent of all gastrointestinal carcinoids) but may actually be more frequent (31 percent) (Solcia et al. in this symposium). They are not dependent on hypergastrinemia and have a high metastatic potential (55 percent), including distant metastases [62]. The multi-centric carcinoids associated with hypergastrinemia are usually small and located within the fundus corpus. They have a low tendency to metastasize, mainly to regional lymph nodes (6–22 percent) [6,11,61,63]. The multi-centric gastric carcinoids in man thus have several features in common with spontaneous and drug-induced carcinoids in *Mastomys*. Sporadic gastric carcinoids in man, on the other hand, are invariably solitary tumors located in the fundus/corpus region and are thus distinctly different from the gastric carcinoids in *Mastomys*.

Morphologically, human and *Mastomys* carcinoid tumors also display great similarities. All gastric carcinoids in man and in *Mastomys* are invariably argyrophilic when stained with the Grimelius technique and immunopositive when stained with antisera against chromogranin A [11–13]. The Masson silver reaction is usually negative, but small numbers of serotonin-, gastrin-, somatostatin-, or pancreatic polypeptide immunoreactive tumor cells have been reported to occur in human gastric carcinoids, while gastric carcinoids in *Mastomys* have been shown to contain a small population of peptide YY (PYY) and enteroglucagon storing cells [12,13,24,61]. Ultrastructurally, human gastric carcinoids are predominantly made up of ECL cells with typical secretory granules. A variable number of other gastric endocrine cells, e.g., EC, D, X, P, G, and PP cells, may also be found [12,13]. Ultrastructural analysis of carcinoid tumors in *Mastomys* has also demonstrated that a majority of the tumor cells are of ECL-cell type, although other cell types may also be encountered [24,28,40,46,47] (Fig. 1). Biochemical identification of the hormonal contents of human gastric carcinoids has been incomplete, but there are reports demonstrating histamine production by tumors as well as increased urinary excretion of methylimidazole acetic acid (MeImAA), a major metabolite of histamine [7,8,64]. The methodological difficulties involved in the histochemical or immunohistochemical demonstration of histamine [65] may suggest that the frequency of histamine-

producing human gastric carcinoids may have been underestimated. Gastric carcinoids in *Mastomys,* on the other hand, regularly produce large amounts of histamine, which may be responsible for such symptoms as flushing and gastric/duodenal ulceration. Patients with CAG type A or Zollinger-Ellison with MEN-1 and gastric carcinoids have characteristic "precursor lesions" in the non-tumoral gastric mucosa. Such precursor lesions include hyperplasia and dysplasia of gastric endocrine cells, e.g., linear, micronodular, or microinvasive growth [13,49]. The same characteristic growth patterns are also observed among gastric endocrine cells in *Mastomys* subjected to long-term treatment with histamine$_2$-receptor blockers [41], which points to similarities in histogenesis of these tumors. The structural and biochemical similarities between human and *Mastomys* gastric carcinoids thus suggest a common histogenesis with transformation of ECL cells into gastric carcinoids during prolonged hypergastrinemia.

The importance of hypergastrinemia for the development of gastric carcinoids has led to experimentation with the surgical treatment of these patients. The multicentric carcinoids were initially treated with total gastrectomy, but, if gastrin is a crucial growth factor for these tumors, a lesser surgical procedure, e.g., antrectomy, would be adequate treatment to reverse the hyperplasia of the ECL-cell system [3,8,66]. Spontaneous resolution of two cases has been reported [2]. Recently, rapid regression of ECL-cell carcinoids following antrectomy was reported in three patients with pernicious anemia [10]. Urinary excretion of MeImAA, the main histamine metabolite, may serve as a tumor marker for gastric carcinoids: slightly elevated levels were seen in patients with ECL-cell tumors, while the tumor burden in gastric carcinoids of the sporadic type was well reflected by the MeImAA levels [67]. These tumors also have a deficiency of aromatic amino acid decarboxylase, leading to excessive secretion of 5-HTP and secondarily high 5-HIAA excretion after synthesis of 5-HT and degradation in the kidneys.

CONCLUSION

Gastric carcinoid tumors of *Mastomys* share several morphological and biochemical features with human gastric carcinoids. In man, different types of gastric carcinoid exist; especially those occurring in patients with CAG type A or Zollinger-Ellison syndrome with MEN-1 show similarities with the *Mastomys* tumors. Distinctive properties such as argyrophilia, chromogranin A, and typical secretory granules as well as characteristic precursor lesions suggest that a majority of these tumors originate from gastric ECL cells. Furthermore, there appear to be common mechanisms in the pathogenesis of these tumors. Hypergastrinemia invariably accompanies gastric carcinoids in patients with CAG type A and Zollinger-Ellison syndrome with MEN-1, suggesting an important role for gastrin in the development of these tumors. Experimentally induced hypergastrinemia, e.g., by histamine$_2$-receptor blockade, has also been shown to increase the development of carcinoid tumor in *Mastomys.* Against this background, it is of utmost importance to take advantage of the *Mastomys* model in order to elucidate the cellular mechanisms responsible for the proliferation of gastric endocrine cells. In addition, the *Mastomys* model can be utilized to perform reversibility studies, using chronic treatment with potent gastric acid inhibitors, and to study if reversal of endocrine cell hyperplasia, or even of dysplasia/neoplasia, may occur after cessation of treatment.

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