

## AGING AND CANCER OF THE STOMACH AND COLON

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### 1. ABSTRACT

Although the incidence of most human malignancies including cancer of the gastrointestinal tract increases dramatically with advancing age, the precise role of aging in that increase remains a matter of continued controversy. Many probable explanations for the age-related rise in cancer incidence have been offered including altered carcinogen metabolism and the cumulative effects of protracted exposure to cancer-causing agents. Neoplasia of the stomach or colon is a multi-stage process with hyperproliferation being central to the initiation of carcinogenesis. Since aging is associated with increased gastrointestinal mucosal cell proliferation, the possibility that aging itself may render target cells more susceptible to carcinogenic transformation continues to be an area of intense interest and study. This review will examine the evidence for age-related alterations in the structural and functional properties of the gastric and colonic mucosa in an effort to further elucidate the potential mechanisms of carcinogenesis which may be involved during the aging process.

### 2. INTRODUCTION

Life may be considered as an internal homeostatic milieu wherein the visceral components of an organism have the functional capacity to adjust or compensate, within clearly defined limitations, for any metabolic or physiologic imbalance to which the organism is subjected (1). Alternatively, aging represents the accumulation of changes with time which are associated with or are responsible for an ever-increasing susceptibility to disease and ultimately, death (2). As visceral compensatory reserves diminish with time, so does the organism's ability to restore homeostasis when challenged by even the slightest perturbation suggesting that death is inevitable, even in the absence of disease. Within the past 50 years the number of people over the age of 65 years, particularly in developed countries, has increased considerably. In the United States, 1 out of every 10 citizens are now over the age of 65 years, and it is projected

that by the end of this century about 15% of the population will be over 65 years.

Although the incidence rate of most human cancers increases profoundly with advancing age of the host, the specific role of aging in relation to that increase remains the subject of continuing debate and controversy. Is the aging process itself inherently carcinogenic? Does aging enhance carcinogenic susceptibility, or does an increased cancer incidence with time merely reflect of a protracted exposure to carcinogenic agents? (3). Numerous endogenous processes inherent to both aging and carcinogenesis implicate potentially shared derangements in the pathway to tumor formation. These include alterations in DNA methylation, proto-oncogene expression, chromosomal fragile sites, DNA mismatch repair, immune system dysfunction, and free radical reaction damage (4).

Cells of the gastrointestinal (GI) tract mucosa are subject to a constant process of renewal, which in normal adults reflects a balance between proliferation of precursor cells and exfoliation of surface cells (5-7). The mucosa of the GI tract actually has one of the most rapid cell turnover rates of any tissue in the body. The continuous cell renewal is maintained by the sustained proliferative activity of a small number of mucosal stem cells (5,6,8). The proliferative zone is comprised of actively dividing cells distinct from the stem cell, while in a larger non-proliferative zone, cells are undergoing progressive differentiation before being extruded into the lumen. Cell production not only compensates for cellular shedding from the surface epithelium but also assures the renewal of certain specialized cells in the glandular tubes. Any dysfunction in this process may accelerate or diminish the growth rate resulting in either hyperplasia/hypertrophy or atrophy of the organ, respectively. A knowledge of normal cell proliferation kinetics and regulation of GI mucosal growth at various stages of life is, therefore, essential for the understanding of the pathogenesis of many GI mucosal diseases and disorders linked to aging including cancer.

### 3. STOMACH

The gastric mucosa is composed of numerous exocrine and endocrine cells (7) which have different rates of renewal. The mucosa itself is generally subdivided into fundic and antral types. In the oxyntic gland area within the fundic zone, most of the newly produced cells migrate rapidly to the surface while differentiating into mucus secreting cells. The migration time, which represents the time for replacement of the total cell population above the dividing zone, is about 3 days in adult rats (5) and about 4-6 days in humans (9). Parietal (oxyntic) cells, which are generally localized to the mid and upper portion of the fundic glands, are unable to divide (9). Newly formed cells can produce intrinsic factor or slowly migrate down the gland to differentiate into acid producing cells (9). Zymogen (chief) cells, predominately located in the body of fundic glands, secrete pepsinogens and are generally replaced by mitosis (11,12). In the antral region, G cells producing and secreting gastrin and D cells producing somatostatin constitute the endocrinologic repertoire of the gastric mucosa.

Aging is associated with marked changes in the functional and structural properties of the gastric mucosa. In rats, aging is associated with gastric atrophy, as evidenced by a significant reduction in mucosal glandular height, gland density and total mucosal DNA content (13,14). Murine studies have also shown ultrastructural degenerative changes in both parietal and chief cells (14,15), explaining in part the diminished basal and gastrin-induced acid secretion observed in this model (13,14,16). In contrast, recent studies in healthy humans show no significant change in either basal or stimulated gastric acid output specifically related to aging (15,17,18). Although a decline in acid secretion is indeed observed in the elderly, this decrease is primarily related to the higher prevalence of chronic atrophic gastritis in this age group. An additional factor that may influence gastric acid secretion in humans is *Helicobacter pylori* infection. *H. pylori* is recognized as a causative factor in the development of Type B chronic active gastritis and peptic ulcer disease (19,20). Moreover, chronic infection with *H. pylori* may have a role in the evolution of chronic atrophic gastritis (21-24) and may be associated with the development of gastric carcinoma (25,26). Whether aging alone results in gastric mucosal atrophy or whether chronic antral gastritis associated with *H. pylori* evolves over time into chronic atrophic gastritis is the subject of continuing debate. Additionally, the increased prevalence of *H. pylori* with aging may indeed represent a cohort effect (27) as younger populations are showing a decreased seroprevalence with aging.

The prevalence of gastric and duodenal ulcers is high in patients with *H. pylori* infection, suggesting an involvement of this bacterium in peptic ulcer formation (19,20,28,29). Persistent *H. pylori* infection also delays ulcer healing (28). Although the precise mechanism is not fully understood, the cytotoxin Vac A produced by *H. pylori* may inhibit proliferation and migration of epithelial cells (30,31), processes that are essential for mucosal

healing (32). Moreover, Vac A interferes with EGF binding to its receptor, thereby inhibiting EGF or TGF- $\alpha$  - induced proliferation and migration of epithelial cells during ulcer healing (31,32). Delay in ulcer healing in *H. pylori* -infected patients is likely to expose the damaged mucosa to further cellular injury and DNA damage and thus may induce the process of carcinogenesis.

*In vivo* data utilizing proliferating cell nuclear antigen (PCNA) and bromodeoxyuridine labeling (BrdU) suggest that *H. pylori* increases gastric mucosal epithelial cell proliferation (33-35), while *in vitro* data in a differentiated human gastric cancer cell line show diminished proliferation and increased apoptosis (36). Wagner et al (36) hypothesize that in *H. pylori*-induced gastritis, enhanced apoptosis in the superficial portion of the mucosa induces a compensatory hyperproliferation with an increased rate of cell turnover. Subsequently, increased *H. pylori* numbers or an exaggerated immune response may result in excessive apoptosis and/or inhibition of epithelial proliferation ultimately resulting in cell loss or atrophy. It is also noteworthy that diabetic patients have a higher prevalence of *H. pylori* (37), which may explain, at least in part, the increased incidence of gastric mucosal atrophy in long-standing diabetes mellitus (38).

Atrophic gastritis and its associated intestinal metaplasia are age-related lesions and are considered to be precancerous (39). Aged individuals with atrophic gastritis and intestinal metaplasia are statistically at risk of developing gastric cancer, but precise surveillance recommendations have not been determined. Patients who had partial gastrectomy 15-25 years earlier for peptic ulcer disease are at increased risk for gastric cancer (40). We have analyzed time-dependent changes in ornithine decarboxylase activity (ODC), an indicator of mucosal proliferation, in the gastric mucosa of subjects who underwent Billroth I or II gastrectomy (41). We reported that ODC activity was significantly higher in Billroth II patients in whom gastrectomy had been performed > 15 years earlier compared with those in whom it had been performed < 15 years earlier or in normal controls (41). We subsequently examined the frequency of *H. pylori* in post-gastrectomy remnants and noted a 58% frequency in Billroth II patients which was associated with a more severe histologic gastritis (42).

As mentioned previously, the structural and functional integrity of the mucosa of various portions of the GI tract, including the stomach, are maintained by the constant renewal of cells. A number of laboratories, including our own, have studied the age-related changes in GI mucosal cell proliferation and the regulation of this process at different stages of life. We reported that gastric mucosal proliferative activity in rats, as reflected by DNA synthesis, thymidine kinase activity, and protein synthesis, remained elevated during the first 2 weeks of postnatal life and then decreased over the next 2-3 weeks (43). Despite this decrease in proliferative activity between 4-5 wks of life, mucosal DNA content increased dramatically during this period, indicating an increase in total mucosal cells

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(43). In contrast, gastric mucosal proliferative activity in 20-24 month old Fischer rats was found to be higher than in their 4-5 month old counterparts (44) as reflected by increases in mitotic labeling (13,45), rate of DNA synthesis (46,47), thymidine kinase activity (47,48), and ODC activity (43,48). More interestingly, however, the increased mucosal proliferative activity was not accompanied by a concomitant rise in mucosal growth, but rather aging resulted in atrophy as evidenced by decreased mucosal height as well as DNA and RNA content in older animals compared to their younger counterparts (13,45). Whether the diminished mucosal height resulted from increased apoptotic activity or a block in mitosis or other cell cycle regulatory events remains to be determined.

Over the past two decades abundant evidence has accumulated showing that several GI hormones/growth factors, most notably gastrin, bombesin, epidermal growth factor (EGF), and transforming growth factor alpha (TGF- $\alpha$ ), regulate mucosal cell proliferation in the GI tract (49). Although aging is associated with increased mucosal proliferative activity in various tissues of the GI tract, this phenomenon in the gastric mucosa this could not be attributed to increased responsiveness to gastrin, bombesin, EGF or TGF- $\alpha$  (46,47,50,51,52), each of which stimulates mucosal cell proliferation at earlier stages of life (49,53). In fact, we have observed that aging is associated with a loss of responsiveness of the gastric mucosa to the trophic action of both gastrin and bombesin (46,51), while EGF and TGF- $\alpha$  actually inhibit mucosal proliferative activity in aged rats (47,52). Although reasons for this are not fully understood, the age-related loss of responsiveness of the gastric mucosa to the trophic action of gastrin could be related in part to a decrease in the number of gastrin binding sites in the gastric mucosa (54). Whether a similar phenomenon is responsible for the age-related loss of the trophic action of bombesin in the gastric mucosa remains to be determined. Our observation that administration of pharmacological doses of either EGF or TGF- $\alpha$  inhibits gastric mucosal proliferative activity in aged rats (47,52) could partly be related to increased sensitivity of aged gastric mucosa to the EGF-family of peptides. Under such circumstances low doses of these peptides are stimulatory to proliferative processes while higher doses are inhibitory (50,52). Support for this postulation comes from our recent observation that the concentrations of EGF and TGF- $\alpha$  required to induce maximal stimulation in EGF-receptor (EGFR) tyrosine kinase activity in gastric mucosal membrane preparations from aged rats was a fraction of that required for the same induction in young rats (52).

In order to further understand the intracellular events regulating the age-related rise in gastric mucosal proliferative activity, we have assessed the role of tyrosine kinases, enzymes which are known to play a critical role in cell proliferation and differentiation (55,56). Our observation that the age-related increase in gastric mucosal proliferative activity is associated with a concomitant rise in total tyrosine kinase activity and tyrosine phosphorylation of a number of mucosal membrane proteins is indicative of a potential role for this enzyme in regulating mucosal proliferation during aging (13). Since

tyrosine kinases are associated with a number of growth factor receptors and products of many protooncogenes, we also examined the age-related changes in activation of certain receptor and non-receptor tyrosine kinases with particular reference to pp60<sup>c-src</sup> and EGFR. Our observation that the increased gastric mucosal proliferative activity with aging is accompanied by a concomitant rise in tyrosine kinase activity and expression of pp60<sup>c-src</sup> and EGFR suggests an involvement of these enzymes in the regulation of GI mucosal cell proliferation during aging (45,57). A similar phenomenon was also noted for c-erbB-2, the structural and functional homologue of EGFR which also possesses tyrosine kinase activity (57). Since ligand binding is one of the primary causes for activation of intrinsic tyrosine kinase activity of EGFR, we also examined the expression of TGF- $\alpha$ , one of the primary ligands of EGFR, in the gastric mucosa during advancing age. We observed 2-3-fold higher steady-state mRNA levels of TGF- $\alpha$  in the gastric mucosa of 24-month (aged) Fischer-344 rats than in their 4- and 14-month old counterparts (57). In addition, we also noted that levels of the 18 kDa precursor form of TGF- $\alpha$  in gastric mucosal membranes from aged rats was 400-500% higher than in young animals (57). Since a transmembrane TGF- $\alpha$  precursor form(s) is known to activate EGFR (58), we hypothesized that the membrane-bound form(s) of TGF- $\alpha$  may be responsible for regulating the age-related rise in EGFR tyrosine kinase activity in the gastric mucosa through an autocrine/juxtacrine mechanism. Further experiments are undoubtedly necessary to fully elucidate the role of membrane-bound TGF- $\alpha$  in regulating EGFR-induced signal transduction process(es) in the GI mucosa during aging.

More recently we have observed that stimulation of gastric mucosal proliferative activity, whether the result of aging, injury, or administration of gastrin, EGF, or bombesin to young adult rats, is associated with a marked rise in tyrosine phosphorylation of a membrane protein with an apparent molecular mass of 55kDa (47, 48, 51,59). More importantly, the dose of EGF that inhibits gastric mucosal proliferative activity in aged rats also causes a reduction in tyrosine phosphorylation of this 55-kDa membrane protein, an effect contrary to that observed in young animals (47). We have subsequently raised polyclonal antibodies against this 55-kDa phosphotyrosine membrane protein in an effort to further characterize it. The subsequent purification and immunoprecipitation studies showed that the 55-kDa gastric mucosal membrane protein to be a tyrosine kinase and with substantially higher activity in aged compared to young rats (60). We have also noted that stimulation of murine gastric mucosal proliferative activity 24 hours after injury is accompanied by a marked rise in the relative abundance of immunoreactive 55-kDa protein in the mucous neck area of the gastric mucosa (60). We plan to further explore the role of this protein in regulating gastric mucosal cell proliferation in response to various GI hormones/growth factors.

## 4. COLON

Normal aging has diverse effects on the large intestine with alterations in mucosal cell growth,

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differentiation, metabolism, and immunity. The alterations that have evolved in the physiologic process of aging must be differentiated from those that are sequelae of age related pathogenic processes. One consistent pathologic observation in senescent animals and humans is the increased incidence of colorectal cancer, a leading cause of morbidity and mortality with more than 150,000 newly diagnosed cases annually in the U.S. alone (61). Explanations have been offered for the age-related increase in colon cancer incidence such as altered carcinogen metabolism and the cumulative effects of long-term exposure to certain cancer causing agents (62-64). Nevertheless, there is an accumulating body of evidence indicating that aging itself is associated with alterations in cellular proliferation and enhanced susceptibility to transformation upon exposure to carcinogens. Although colorectal neoplasia is clearly a multistage process, hyperproliferation is believed to be central to the initiation of carcinogenesis (65). Holt and Yeh (66) have demonstrated that the crypt cell proliferation rate is significantly higher in older rats compared to their younger counterparts. Furthermore, a widening of the crypt zone of proliferating cells was also noted. Finally, although withdrawal of food normally induces a rapid reduction in indices of crypt cell proliferation in the colon of rodents, younger animals had a significantly more pronounced reduction when compared to older animals (66).

Several genetic alterations have also been observed, further emphasizing a link between colon cancer and aging. Hastle *et al.* (67) examined telomere length in relation to age and colon adenomas, the precursors of colon carcinomas. Telomeres are believed to be critical in the maintenance of chromosomal integrity and are composed of a sequence of six nucleotides (TTAGGG) which is repeated from several hundred to a thousand times (68). These sequences are synthesized by telomerase, a ribonucleoprotein enzyme composed of both protein and RNA. Telomerase makes a DNA copy of its own RNA sequence by reverse transcription. The extension of telomeres by telomerase is necessary to offset the normal shrinkage of chromosomes that occurs after each DNA replication. Hastle *et al.* (68) noted a reduction in telomere length in normal colonic tissue of older compared to their younger individuals. Length reductions were also seen in colon adenomas and carcinomas. They hypothesize that telomere loss may render chromosomes less stable and impair viability. Alternatively, they may make chromosomes more prone to fusion bridge breakage cycles, leading to daughter cells which receive partly deleted and duplicated chromosomes. These alterations may have a role in generating loss of alleles of restriction fragment length polymorphisms that often occur in colorectal cancers (69). Along similar lines, Issa *et al.* (70) studied the estrogen receptor (ER) in relation to aging and colorectal cancer. The ER may actually serve as a tumor suppresser gene in that it is expressed in normal tissue, altered in tumors, and suppresses growth in tumor cell lines and tissues. CpG islands located in the promoter region of genes are normally free of methylation, but methylation is common in islands of the ER in aging, colonic mucosa and in colon tumors (68). Moreover, methylation of the ER

in older healthy patients or those with colon cancer is associated with inactivation of the gene.

To further explore the age-related susceptibility of the colonic mucosa to carcinogens, we recently examined the *in vitro* changes in ornithine decarboxylase (ODC) and tyrosine kinase activity in the colonic mucosa in response to methylazoxymethanol (MAOM), the active metabolite of the colonic carcinogen azoxymethane(AOM). We observed a greater degree of stimulation of ODC and tyrosine kinase activities in aged than in young colonic mucosa in response to MAOM (71), indicating an increased susceptibility of the colonic mucosa of aged rats to this carcinogen. A similar phenomenon was observed with TGF- $\alpha$  (72), a potent mitogen for various tissues of the GI tract including the colon (73,74). A growing body of evidence also suggests that TGF- $\alpha$  may play a critical role in the development of colorectal neoplasia through autocrine/paracrine mechanisms supported by the observation that cell lines derived from adenocarcinomas of various tissues, including the colon, show increased expression of TGF- $\alpha$  and its receptor, EGFR (75-79). Since TGF- $\alpha$  exerts its mitogenic action by activating the intrinsic tyrosine kinase activity of EGFR, we compared the changes in TGF- $\alpha$  mediated activation of EGFR-associated tyrosine kinase between young and aged rats (72). Despite a higher basal EGFR tyrosine kinase activity in the colonic mucosa of aged rats, TGF- $\alpha$  produced a significantly greater stimulation of EGFR tyrosine kinase activity and tyrosine phosphorylation of EGFR and several other mucosal proteins. Since this occurred despite a higher basal EGFR tyrosine kinase in aged rats, we suggested that aging is associated with increased responsiveness of the colonic mucosa to TGF- $\alpha$  (72). A similar observation was also made with isolated colonocytes from AOM-treated rats. Both EGF and TGF- $\alpha$  caused a comparatively greater degree of stimulation of EGFR tyrosine kinase in colonocytes isolated from rats 5 days after a single injection of AOM than those from control animals (80). Moreover, one of the phosphorylated proteins was the previously discussed 55 kDa protein, further implying a role for this phosphoprotein in GI mucosal cell proliferation and/or GI carcinogenesis. Taken together, these alterations in GI mucosal proliferation and differentiation strongly suggest that aging may predispose the colon to malignant transformation.

## 5. ACKNOWLEDGMENT

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