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HYPOTHESIS

Biologic Correlates of Paraneoplasia and Preneoplasia in Gastritis

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ABSTRACT. Dynamic evolution of injury to the mucosa of the stomach appears to operate as inflammatory consequences, as delineated by regional distribution in the antrum or gastric corpus in particular. Paraneoplasia and preneoplasia appear representations of such distribution pattern, and as parametric correlates of onset and progression of a transformation process emanating from surface epithelium and crypt stem cells. Biology of the derived characterization of the mucosal inflammation is represented by multiple superimpositions of various inflammatory states ranging from acute to chronic gastritis, and also gastric mucosal atrophy. In terms that are contributory towards a concept of realized consequence of an inflammatory infiltrate arising within the lamina propria, it might further appear that the distribution patterns of metaplasia are simply representative of dynamics of an onset process in inflammatory involvement of the mucosa. It is only with reference to such consequences as parallel and subsequent development of cell injury that the gastritis proves a phenomenon of persistence rather than simply of intensity of the reactive changes affecting both a primary surface epithelial cell pool and the stem cells that populate the glandular crypts of the gastric mucosa.

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Abbreviations used: H. pylori, Helicobacter pylori

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1. Introduction

Acute gastritis appears to often constitute an acute exacerbation of long-standing chronic inflammation of the gastric mucosa and in terms beyond limitations of the inflammatory cell infiltrate in the lamina propria. *Helicobacter pylori* (*H. pylori*) infection induces CpG island hypermethylation in gastric mucosa (Yoo *et al.*, 2008). Heat shock protein B may be implicated also (DeLuca *et al.*, 2008). It would involve aspects of progression of an injury to the crypt epithelium implicating stem cell differentiation and migration up the crypt.

Metaplasia of the gastric epithelium is one aspect of a whole aggregate of phenomena that constitute an injury as evidenced by systems of specialized differentiation of single cells and of whole categories of cells with injury to the surface epithelium. *H. pylori* is the strongest known risk factor for gastric adenocarcinoma, implicating the Cag secretion system (Franco *et al.*, 2008).

2. Response Phenomena

It might be significant to consider response phenomena in relation to an injury that is redefined as the development of the inflammatory changes involving lamina propria and associated mucosal glands in particular. It would be in terms of systems of progression and as acute exacerbations of chronic inflammatory states that the gastric mucosa further evolves as induced paraneoplastic transformation. Oxidative stress is linked to gastric carcinogenesis because of its ability to damage DNA (Cao *et al.*, 2008).

It might prove especially significant to consider the evolutionary course of a mucosal injury as terms of reference in the subsequent development of the inflammatory infiltrate.

It is significant that intraepithelial lymphocytes are a constituent system of involvement of a columnar epithelial cell layer covering the mucosal gastric surface and glands. *H. pylori* infection accounts for most cases of gastric cancer, but the initiating events remain unclear. Interleukin 11 expression is associated with adenocarcinoma development but not gastritic lesions (Jackson *et al.*, 2007).

It would seem that the involvement of such diverse pathways as represented by allergic and infectious systems would constitute progression allied to dynamic changes in the inflammatory infiltrate in the lamina propria.

It is beyond the delineation of further pathways as redefined systems that allow progression of injury to the crypt stem cells that there evolves a predisposition to carcinogenesis in terms of a paraneoplastic phenomenon rather than as a specific preneoplastic transformation. Gastric carcinoma shows a high frequency of aberrant CpG island hypermethylation (Kang *et al.*, 2007).

Realized systems of modified representation of the injury would involve transformation as pathways of progression beyond defined limits of compromised progression of atrophic gastritis to gastric mucosal atrophy. Dysplasia may precede or accompany invasive neoplasia (Salas Caudevilla, 2007).

The controversial nature of the variable chronicity of the gastric inflammation might simply constitute involvement of the gastric lamina propria as this relates to basic pathways of subsequent progression. Chronic gastritis and chronic atrophic gastritis show enhanced apoptosis independent of *H. pylori* infection, aneuploidy and overexpression of p53 protein (Targa *et al.*, 2007).

One might view the whole phenomenon of onset and progression of an inflammation as constituted by relative consequence and as subsequent transformation of the injury to the crypt epithelium.

3. Classification of Mucosal Inflammation

The classifications of the chronic gastric inflammatory states constitute a variability of developed pathways related to reflux of bile and as Helicobacter pylori infection in the first instance. Aberrant activation of the β-catenin signal promotes intestinal metaplasia due to inherent CagA activity that is independent of the structural polymorphism of CagA (Kurashima *et al.*, 2008). It would further represent systems of conversion of pathways as constituted by injury to

the surface epithelial cells, on the one hand, and to crypt stem cells and crypt epithelium, on the other. Parietal cell atrophy is a known preneoplastic lesion and correlates with loss of sonic hedgehog processing (Zavros *et al.*, 2007). Systems of interactivity as provided by both surface and crypt epithelium would perhaps allow for progression of the injury as mediated primarily by the inflamed lamina propria.

In view of redefinition of the mucosal injury, there might be reemphasized a qualitative representation of the injurious agents as evidenced by the acute neutrophilic component of the inflammatory infiltrate.

In terms of the injury beyond possible consequence as paraneoplastic or preneoplastic transformation, there might further evolve systems of injury allied primarily to the constituted end-pathways of cell replacement and metaplasia.

Chronic gastritis appears to be the background lesion while atrophy and intestinal metaplasia include long-term infection with *H. pylori* (Arif and Syed, 2007).

Metaplasia would allow for conversion of the natural state of senescence of the surface epithelial cells in terms of intestinalization and as transformed nature of the differentiation pathways originating in the gastric mucosal cell populations. Anti-inflammatory cytokines play an important role in the prevention of neoplastic disorders (Sugimoto *et al.*, 2007).

4. Metaplasia and Stem Cells

It might prove particularly significant to recognize systems as represented by metaplasia of the surface epithelial cells and as these develop specifically from the epithelial crypts. Pathogenic mechanisms associated with Helicobacter pylori infection enhance susceptibility of the gastric epithelium to carcinogenic conversion (Hofman *et al.*, 2007).

Stem cells might allow for the development of injury *per se* beyond strict consideration of target cells in the gastric epithelium or mucosa in general. The submucosa in turn would be incorporated within systems of progression of an injury that is primarily targeting the crypt stem cell population.

It would prove especially significant to recognize systems as represented by an injury defined beyond progression of sequential injury to the gastric mucosa.

It might prove highly significant to consider the proliferation of crypt epithelium in terms of the specialized nature of a surface epithelial injury beyond specific involvement of the lamina propria *per se*. Pepsinogen I may be a useful marker in patients with a residual higher risk of gastric cancer after *H. pylori* eradication (Shiotani *et al.*, 2007).

It is in relation to injury both as a derived phenomenon in its own right and as redefined origin of pathways of consequential transformation that the gastric inflammatory state primarily eventuates as injury to the surface epithelium. In such terms, the consequent involvement of crypt stem cells is a secondary phenomenon resulting from ongoing progression of injury and as metaplasia of the surface epithelium.

It appears especially significant to consider revolutionary pathways in terms beyond simple categorization of the injurious event. Both intestinal and diffuse types of gastric carcinoma indicate strong association with *H. pylori* (Arif and Syed, 2007).

It is beyond representation of an inflammatory infiltrate seemingly originating in the lamina propria of the gastric mucosa that there further develops a primary system of established injury to the surface epithelium. Loss of sonic hedgehog and aberrant CDX2 expression are early changes correlating with the presence of intestinal metaplasia occurring in the gastric mucosa prior to neoplastic transformation (Shiotani *et al.*, 2007).

Simplification of the injury as constituted by intestinal metaplastic transformation would particularly represent a possible reperfusion deficit as constituted by active blood supply dynamics involving primarily the mucosal lamina propria.

Reflux of bile is a phenomenon primarily targeting foveolar hyperplasia of the mucosal glands as onset or progression pathways of injury to the lamina propria. One might view gastritis as a composite phenomenon that constitutes integral and sequential representation of

various subcomponent pathways in the evolution of lamina propria reactivity. Aberrant DNA methylation develops in non-neoplastic gastric mucosa in patients infected by *H. pylori* organisms (Perri *et al.*, 2007). Transformation of pathways culminates in evolved patterns of resultant injury as evidenced by dynamics of progression or resolution. Immune responses to *H. pylori* are involved in gastric mucosal inflammation and might affect clinical outcome, including the development of gastric carcinoma (Seno *et al.*, 2007).

5. Predisposing Factors

Predisposition of the variable injury to the surface epithelium would relate also and in particular to lymphocytic components of the inflammatory infiltrate. It is significant that further transformation might at times implicate lymphoid follicular hyperplasia in the gastric mucosa.

Antigen presentation and processing appear component systems in the process of transformation of the crypt epithelium in the first instance and as consequent transformation and metaplasia of the surface epithelium that is particularly associated with stem cell transformation.

It is in terms of the stem cell involvement of the various pathways representing targeted cellular populations in gastritis that subpopulation progression proceeds as mucosal injury. Distinct host cytokine responses in the gastric mucosa might have a role in *H. pylori*-induced carcinogenesis (Seno *et al.*, 2007).

Gastritis would constitute further evidence in support of an injury that is defined beyond modes of development and of integration in sustained progression of the gastric inflammation. Aberrant DNA methylation is one of the major events in carcinogenesis (Tahara *et al.*, 2007).

H. pylori represents a spectrum of possible significant outcome and transformation of the kinetics of a dynamic transformation involving biologic identity of the stem cells. Promoter of the p14 gene may be closely associated with *H. pylori* infection when methylated. Methylated p16 gene accumulates with gastric mucosal atrophy and intestinal metaplasia and may associate with the presence of gastric cancer (Tahara *et al.*, 2007). Constituent representation of integral injurious events would implicate pattern-representation of the mucosa of the stomach in terms of regional subspecification related particularly to antral and corpus involvement.

Autoimmune response and induced injury would constitute further evidence in onset and progression primarily represented by evolutionary transformation of epithelial and crypt stem cell populations.

6. Inflammatory Pathways of Consequence

It might prove significant to realize pathways as end-products of systemic representation of an injury primarily targeting the surface epithelium and only secondarily implicating crypt epithelial abnormalities in transformation.

Induced dynamics of progression of an injury to mucosal cells would subsequently constitute integral pathways beyond recognition of such transformation and of metaplasia of the surface epithelium. *H. pylori* induces atrophic gastritis progressing to gastric cancer together with loss of sonic hedgehog and aberrant CDX2 expression (Shiotani *et al.*, 2006).

Foveolar hyperplasia and subsequent emergence of intestinal metaplasia or pyloric metaplasia might represent constitutive mechanisms in the development of further identifiable injury to differentiated end-pathway targets.

The host innate immune response plays an important role in determining outcome of *H. pylori* infection (Hold *et al.*, 2007).

A limited spectrum of possible subsequent injury to surface epithelium would activate pathways of constitutive transformation as evidenced by progression to a state of established chronic gastritis or end-stage gastric atrophy.

The various representations of an associated *H. pylori* infection of the gastric mucosa might allow for progression of transformation not only in terms of metaplasia but especially as relative injury to the crypt stem cells.

The intensity of the inflammatory infiltrate constitutes a primary parameter in development

of an injury to the gastric mucosa and also as constitutive transformation induced as basic cellular and regional injury. MALT lymphoma is a model of how sustained inflammation increases the risk of genotoxic insults and how these genetic events initiate oncogenesis (Sagaert *et al.*, 2007).

7. Antral and Corpus Regionalization

Antral and corporeal injury constitutes regional distribution patterns of an inflammatory involvement as represented by the onset and subsequent progression of an injury as etiologically determined identity in biologic transformation.

An increase in upper endoscopic examinations has allowed recognition of novel patterns and distribution of mucosal injury (Srivastava and Lauwers, 2007).

It is beyond the occurrence of bile reflux as a causative factor inducing gastritis that there would evolve further representation of pathways and of targeted outcome of such mucosal injury. None of the available classifications of gastritis provides immediate prognostic/therapeutic information to clinicians (Rugge *et al.*, 2007).

Paraneoplastic progression of the injury is an outcome phenomenon allied to metaplasia and to preselective targeting of the crypt stem cell subpopulations. It is beyond the limitations of recognized specifications of the injurious events affecting the gastric mucosal subcomponents that there would further evolve systems of constitutive transformation of biologic parameters. It is significant that gastric carcinogenesis is a derived function of combined injury as targeting systems implicating *H. pylori*; the latter is only one component system in the realization of an injury that progresses largely as onset dynamics of an inflammatory infiltration of the lamina propria. Onset progression is interpreted beyond simple dynamics of transformation or of metaplastic intestinalization of the surface epithelium.

Chronic inflammation induces oxidative stress, perturbed epithelial cell proliferation and apoptosis, and also cytokine secretion (Matysiak-Budnik and Megraud, 2006).

One might view the panorama of involvement of the gastric mucosa as terms of reference implicating injury as end-stage dynamics and as established transforming potential. A sequence of *H. pylori* induced chronic superficial gastritis evolves as atrophic gastritis, intestinal metaplasia, dysplasia and eventually gastric cancer (Matysiak-Budnik and Megraud, 2006).

8. Carcinogenesis

Carcinogenesis is implicated beyond the malignant transformation of crypt epithelial cells or of stem cell pathobiology. *H. pylori* infection causes a chronic gastritis that is the precursor to all the pathophysiologic abnormalities characteristic of gastric carcinogenesis (El-Omar, 2006).

Gastric derivation of the metaplastic potential reveals true potential for the regeneration of a gastric mucosa associated with further transformation of the injurious event. Genetic polymorphisms determine disease susceptibility and severity of involvement (El-Omar, 2006).

It is significant to recognize pathways of transformation beyond the realized injurious events. Paraneoplasia is a pathogenic component system beyond definition of recognized cellular subcomponents of the gastric mucosa. Epigenetic dysregulation might constitute a major mechanism for altered gene expression in precursor premalignant stages in gastric carcinogenesis (Vauhkonen *et al.*, 2006).

Pyloric metaplasia and intestinal metaplasia are recognizable representations as projected by a surface epithelium, in the first instance, and as actively propagated beyond the dynamic consequences of transformation *per se*.

It might be particularly in view of the establishment of the mucosal injury that there would further develop defined pathways of carcinogenesis affecting an outcome of intestinal or diffuse morphology to the gastric carcinoma. Promoter methylation may prove an important regulatory mechanism of sonic hedgehog expression (Wang *et al.*, 2006).

The etiology and pathogenesis of a malignant neoplasm are simply superimpositions of different environmental conditioning events be-

yond the realization of mode or form of transformation of crypt stem cells.

In addition, the metaplastic mucosal surface epithelium proves a consequence of an injury that progresses as persistent involvement rather than simply as an increase in intensity of the inflammatory state.

H. pylori-induced dysregulation of β-catenin-dependent pathways may account for an increased risk for gastric cancer conferred by this pathogen (Franco *et al.*, 2005).

Classifications of the chronic gastritis in terms especially of involvement by acute exacerbations of the persistent chronic inflammatory state would represent circumscribed representations of the mucosal injury.

It might prove particularly significant to recognize biologic pathways as themselves end-result lesions that evolve as differentiation of transformed surface mucosal epithelium and crypt stem cells.

It is in terms of an undifferentiated cell subpopulation that a predisposition to carcinoma or to lymphoma of the stomach develops as successive evolution of complex pathogenesis and of targeting of multiple cell types in the gastric mucosa.

The lamina propria would constitute realized evolution of inflammatory activity that allows for the validation of systems of consequence and as derived primary pathways of sequential progression.

9. Concluding Remarks

A definite delineation of the consequences of an injury as portrayed by an inflammatory infiltrate of the gastric lamina propria would help account for progressive transformation and carcinogenesis.

It is beyond the biologic potential of a metaplastic process in induced injury that the stomach would further allow for evolved consequence and as representative of subcomponent foci of inflamed antral and corpus mucosa.

It is in terms strictly represented by the persistently evolving injury to the crypt stem cells that the subsequent involvement of the surface epithelium implicates a targeted consequence to dynamic transformation.

It is in view of such conceptual representation of various forms of cellular injury that carcinogenesis of the stomach constitutes pathways of strictly parallel progression and transformation of represented biologic or pathobiologic identity of such injury.

Potentiality for change in the biology of cellular identity would further evolve in terms represented by a neogenesis that is either intestinal or diffuse in morphologic delineation, and as a consequence to aggregate pathways of metaplasia, carcinogenesis or cell death.

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