Growth Factor Regulation

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The epithelial populations found throughout the gastrointestinal tract exhibit a relatively high rate of turnover throughout postnatal life. The maintenance of normal cellularity in the setting of continuous proliferation, differentiation, and cell senescence implies the presence of exquisite regulation of cell turnover. In addition, regulatory mechanisms must provide plasticity in order to facilitate reconstitution of mucosal integrity following injury. While undoubtedly cell proliferation and mucosal growth are modulated by a wide variety of influences, including extracellular matrix constituents and nutrient availability, it is clear that a number of peptides with growth modulatory properties play an important role in the gastrointestinal tract. Although the full diversity of the peptide growth factors which regulate mucosal growth in the gastrointestinal tract remains to be determined, several important peptide growth factors discussed in this section have been demonstrated to contribute to growth and proliferation in gastrointestinal tract mucosa. From the study of these factors, some general themes of peptide growth factor action in the gastrointestinal tract have emerged. First, growth in the mature gastrointestinal tract is modulated by structurally diverse proteins. Second, these proteins act through a variety of mechanisms. Third, these proteins often exhibit distinct functional properties in addition to their capability to stimulate or inhibit growth [1]. Fourth, these proteins may play essential roles in response to mucosal injury in addition to their role in constitutive regulation of normal mucosal turnover. A corollary of the latter is that alterations in growth factor expression may contribute to the pathogenesis of mucosal disease. A brief overview of observations supporting each of these themes is reinforced by the papers in this section. It should be noted, however, that the delineation of a coherent view of the interrelationships between the various proteins that comprise a network of peptide growth factors will be necessary in order to achieve an accurate estimation of the role of each factor in normal mucosal homeostasis and in pathologic states.

Structural Diversity of Peptide Growth Factors

The various papers in this section underscore the importance of a wide variety of peptides in growth regulation. These include a number of proteins described in this section: epidermal growth factor [2], transforming growth factor α (TGFα) [3] (members of a common peptide family), and fibroblast growth factor, as well as products of the enteroendocrine and classic endocrine elements, as exemplified by gastrin and the insulin family (insulin and the insulin-like growth factors). Although not considered in these papers, additional factors of clear importance are the transforming growth factor β family [4–6], structurally and functionally unrelated to TGFα, and the so-called hepatocyte growth factor. Undoubtedly, additional proteins

Abbreviations:  EGF: epidermal growth factor GI: gastrointestinal ITF: intestinal trefoil factor TGFα: transforming growth factor α

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which modulate growth in the gastrointestinal tract remain to be identified; these may include additional members of these peptide families which have not yet been fully explored in the context of the gastrointestinal (GI) tract (e.g., cripto, a member of the epidermal growth factor [EGF] family). Most important, these may also include categorically distinct groups of proteins expressed largely or exclusively in the gastrointestinal tract. Among potentially important candidates are a family of peptides designated trefoil proteins, which encompass several peptides that are expressed in highly regionalized fashion in the normal gastrointestinal tract, e.g., intestinal trefoil factor (ITF) found only within small and large intestinal mucosa, pS2 found in the gastric mucosa, and SP found in the pancreas, gastric antrum, and duodenum [7,8]. Interestingly, these peptides, characterized by a highly conserved motif, are protease-resistant peptides which are secreted into the lumen, where they may retain biological activity. Despite preliminary studies indicating growth-modulating properties when exposed to established tumor-derived cell lines, however, the relative importance of these effects compared to their other activities, as well as other known growth factors, remains to be determined. Nonetheless, the relatively recent recognition of this family underscores the remaining need to achieve a comprehensive knowledge of the range of proteins which participate in growth control in the GI tract.

**Mechanistic Basis of Growth Factor Action**

It is axiomatic that growth factors effect their activities through interaction with specific high-affinity receptors. These receptors appear to encompass the major classes of cell surface receptors, including (presumably) G-coupled seven membrane-spanning receptors (e.g., gastrin) and receptor-type tyrosine kinases (e.g., EGF/TGFα receptor).

It is clear that the growth factor ligand-receptor interaction effects a regulatory event between a growth factor-producing cell and a target cell that can occur over a spectrum of distances. An important motif, which appears to be especially common in the activities of many growth factors, is the autocrine mechanism, in which a cell expresses both a growth factor and its cognate receptor. This widespread mechanism may provide an important measure of feedback regulation of growth factor expression. Autocrine actions have been demonstrated for TGFα within intestinal epithelial cells and, as discussed in this section, within the gastric mucosa. At least one factor, TGFα, expressed initially as a membrane-bound cell surface molecule, can interact directly with receptors on an adjacent cell, a mechanism designated juxtacrine regulation. An especially important mechanism of growth factor action is the capacity to modulate cells in the microenvironment through local secretion, a mechanism designated paracrine regulation; it appears that virtually every peptide exerts a variety of effects through paracrine actions. It is evident that a given peptide may utilize more than one of these mechanisms as exemplified by TGFα, which utilizes all of these modes. Finally, it should be noted that some trophic factors act at a more extended distance in a classical hormonal fashion, for example, gastrin.

**Diversity of Functional Properties of Peptide Growth Factors**

Among the peptides found to possess growth factor activities at sites within the GI tract, many have additional functional properties. In many instances, it is not possible to know a priori the relative importance of these different activities. This
paradox is exemplified by both TGF\(\alpha\) and EGF. In addition to their ability to stimulate proliferation, each may also serve as a potent inhibitor of gastric acid secretion. In contrast, gastrin appears to be trophic for gastric mucosa yet is a potent stimulus for gastric acid secretion. Although, as noted above, the full range of functional activities of the trefoil family remain to be determined, available information suggests that they too exhibit significant properties in addition to any growth modulatory activities.

Indeed, in recent years a large number of proteins expressed by various mucosal and submucosal cell populations in the stomach and intestine, which have been primarily identified on the basis of their abilities to influence specific target cell functions, have been recognized to have at least circumscribed growth factor activities. These proteins include many cytokines that integrate immune and inflammatory responses which have been found to alter proliferation of epithelial and other cell populations, such as TGF\(\beta\) [9]. A comprehensive knowledge of the functional properties of peptides with growth factor activity will be essential before an understanding of the manner in which this complex and redundant network achieves integrated regulation of growth and response to injury. The close interaction of the growth factor activities of different peptides is illustrated by the striking alterations in pancreatic growth and development in mice bearing transgenes for gastrin and TGF\(\alpha\) when contrasted with the essentially normal development of the pancreas in lines bearing only one of the transgenes, as discussed in one of the papers in this section.

*Role of Growth Factors in Injury*

The role of growth factors in sustaining the constitutive high level of turnover characteristic of mucosa throughout the gastrointestinal tract remains unclear in many fundamental features, as highlighted above. Progress in clarifying these features will be necessary before the role of growth factors in repair following injury can be understood; however, a number of observations already underscore the importance of growth factors in mechanisms of mucosal reconstitution and perhaps through relative deficiency in the mechanisms of injury itself. The former concept is supported by the apparent induction of growth factor expression in proximity to sites of injury. The marked enhancement of multiple trefoil factors in cells immediately adjacent to ulcerated mucosa from patients with either peptic disease or Crohn's disease has been suggested by one of our contributors to be the most compelling observations supporting the notion that these peptides serve as growth factors [10]. Wright et al. suggest that distinctive cells dedicated to growth factor production may emerge at the site of mucosal injury [11]. The potential importance of growth factors in mucosal injury and repair are directly indicated by the observations of Szabo and his co-workers, which suggest that reduced concentrations of basic fibroblast growth factor may be an important permissive event in the development of mucosal ulceration in the gastrointestinal tract.

The role of other growth factors may be indirect as well as direct. Thus TGF\(\alpha\), a peptide which could contribute to repair through stimulation of epithelial proliferation, may also facilitate repair through promoting angiogenesis. The effects of other peptides on tissue repair following injury cannot be easily predicted in the context of the pleomorphic spectrum of multiple functional properties (which may be, in part, situational and determined by the ambient mixture of other factors) of the individual
growth factor. This fact is illustrated by recent studies in our laboratory evaluating the effects of TGFβ on repair of model wounded monolayers of a rat intestinal epithelial cell line [6]. Although this factor inhibits proliferation, it was found to promote re-epithelialization of wounded areas through the stimulation of cell migration.

Summary

As the various features of growth factor action in the GI tract noted above indicate, collectively these peptides form a network which helps to preserve mucosal integrity. An important characteristic of that network, which has already emerged from this still fragmentary definition of its dimensions, is the redundancy present on several planes. Multiple factors appear to have overlapping functional properties. Conversely, each peptide appears to have multiple biological activities. Though not considered in this section, in several instances a peptide growth factor may have more than one specific cell receptor, and, conversely, there appears to be at least some promiscuity in receptor specificity, as exemplified by the overlapping receptors for the peptides of the insulin family and the common recognition of EGF and TGFα by a single receptor. At the cellular level, each factor may be expressed by several distinct cell types and, conversely, may have multiple cellular targets. Much future work will be needed to determine fully the functional features of this redundant network. It will first depend upon continued intensive characterization of the full spectrum of individual growth modulatory peptides and their mechanisms of action.

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