Gene expression in Barrett’s mucosa: acute and chronic adaptive responses in the oesophagus

The oesophagus is of major interest in the biological study of the alimentary tract in that the epithelial cells have a remarkable ability to adapt to chemical and mechanical injury. In particular, the induction, promotion, and progression of normal or inflamed squamous oesophageal epithelium to Barrett’s mucosa and ultimately adenocarcinoma as a result of chronic gastro-oesophageal reflux disease has varied but distinct morphological stages suitable for the study of sequential gene expression. Some of the cellular mechanisms for adaptation which underlie this latter process are now known.

Squamous oesophageal cells are highly sensitive to refluxed gastric acid and intrusive inflammatory cells: cell loss and necrosis are the earliest histological findings. In this regard one of the early ‘adaptive’ responses to increased cell loss in reflux oesophagitis is an increase in the proliferative zone height to maintain or even, in some individuals, increase epithelial thickness by trophic stimulation of epidermal growth factor (EGF) contained in the adjacent endothelium. Another mechanism, poorly understood until recently, is the increase in the proliferative zone length by the exaggeration of the folds in the basal epithelium (papillae formation) to enable an increased proliferative compartment to generate and maintain the same size of superficial (differentiated) epithelial compartment.

These latter adaptive changes also occur in other squamous epithelia and it can be interpreted, therefore, that the proliferative organisation of the oesophagus and the skin are generally similar. In one regard, however, their respective organisation may be very different as is seen in the location of the putative epithelial stem cells in epithelial ‘down growths’ in hyperproliferative states, the papillae (in the oesophagus) and then rete pegs (in the skin). The oesophageal stem cells in the proliferative zone, as a rule, proliferate more slowly and do not migrate to maintain their ‘niche’ in the epithelial/mesenchymal interface whereas their progeny (the transit amplifying cells) divide and migrate sideways, upwards, and during inflammation, probably downwards also into deeper layers. As a result, during vigorous proliferation the basal layer folds where the stem cells are located because the daughter cells migrate away from the stem cells (proliferative flux) and may in addition create ‘expansive pressure’ because they are more actively dividing. Therefore, the epithelium immediately above the putative stem cells in the papillae may be much thinner than that above the daughter cells in the inter papillary layer (the opposite to the skin). In this regard the functional stem cells remain in a relatively superficial position in the epithelium making them far more accessible to refluxed chemical mutagens permeating through the thin upper layers than their counterparts in the flat basal layer. Paradoxically, the more severe the reflux the higher are the papillae and hence the more likely are the stem cells to be damaged.

It seems that this latter development may potentially underlie the subsequent promotion of acid resistant lineages (gastric metaplasia) because the non-resistant oesophageal stem cells (or possibly also the stem cells of the submucosal oesophageal glands) are either damaged or die, whereas others which have the ability to redifferentiate to a mucin secreting phenotype survive. In addition, there is indirect evidence to suggest that if mixed gastric and duodenal contents or duodenal contents alone are refluxed then the resulting epithelium will consist of an intestinal phenotype as these cells are bile resistant lineages (intestinal metaplasia). Furthermore, it has previously been shown that bile may either be more directly noxious to the oesophageal cell proteins (including perhaps also the DNA) than acid and may also generate abnormal nucleic acid metabolism making these cells more liable to death or serious epigenetic or genotoxic damage. In this regard, the usual site for the intestinal metaplasia is at the most proximal edge of the Barrett’s mucosa, furthermore from the stomach and nearest the mouth where the pH will be either neutral or alkaline, partly because of alkaline saliva so that pancreatic enzymes will be most biologically active. As a result the oesophagus is selectively replaced by metaplastic cells expressing different phenotypes according to the type of refluxed contents. These metaplastic epithelia are apparently regulated by autocrine mechanisms (usually by action of transforming growth factor alpha (TGFα)) but are not autonomous (partially transformed cells).

In Barrett’s metaplasia at least one novel cell lineage is identifiable in between the true metaplastic epithelium especially near sites of active or previous ulceration. This lineage is morphologically and phenotypically similar to those observed immediately adjacent to other chronic gastrointestinal ulcers, for example in peptic ulcer and Crohn’s disease. The lineage consists of glandular structures which secrete large amounts of EGF and additional peptides (including the Trefoil peptide family), with putative growth regulatory actions, into the superficial compartments of adjacent metaplastic glands.
As a result, the Barrett’s metaplastic glands receive trophic stimulation both from endogenous peptides and an exocrine supply. In most Barrett’s metaplastic glands the epithelium is stable and grows in synchrony with surrounding squamous epithelium and oesophageal glandular mucosa. In approximately 30% of cases the epithelium does not change to a homogeneous phenotype and this is characterised by an ‘incomplete’ intestinal epithelium with both gastric foveolar and intestinal goblet cells and enterocytes. It seems that in this latter phenotype glandular tissue may be generated by stem cells with aberrant differentiation or competing stem cell lineages because heterogeneous phenotypes are present in the same gland. In addition glands have aberrant proliferative control evidenced by the observation of the characteristic extended or abnormal proliferative zones associated with increased growth factor expression. Subsequently some of these cells may become fully transformed and hence express an ‘abnormal’ phenotype visibly different from surrounding cells by promotion of dysplastic clones, in part, by expression of oncogenes especially c-erbB2.

As this process continues, the probability of regression diminishes and cells may ultimately progress to metastases, partly because of the disruption of the final regulatory barrier (negative feedback control by transforming growth factor beta (TGFβ), tumour necrosis factor (TNF) and p53).

In summary, oesophageal squamous epithelium adapts to increased chemical damage and cell loss by acute and chronic responses. In the former the oesophagus increases the growth fraction (number of cells dividing) by hyperplasia and elongation of the proliferative compartment. The chronic response occurs when the initial increase in cell proliferation fails to compensate for the cell loss. In this regard there is subsequent selection of specialised lineages of columnar mucosa partly as a result of change in the phenotype of the relatively exposed squamous (or glandular) stem cells. Each lineage has specific functions, such as the protection against acid (gastric metaplasia), protection against bile (intestinal metaplasia), and repair of ulceration (present in up to 30% of patients with Barrett’s mucosa) (the ulcer associated cell lineage). It may be that these differences in proliferative organisation between the skin and oesophagus explain why metaplasia and cancer are relatively rare in response to contact carcinogens in the former but common in the latter epithelium. As has been suggested in some other epithelial cancers the oesophageal stem cells are possibly the initial target for carcinogens and therefore these cells in particular require urgent study in the future as this disease is increasing dramatically in the western world.

It is seen, therefore, that the range of oesophageal adaptive responses to environmental stimuli is diverse but that the identification of these serial events forms a unifying hypothesis which has important clinical and research implications.