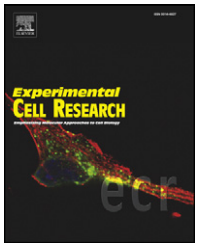
EXPERIMENTAL CELL RESEARCH 317 (2011) 2759–2764

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/yexcr



Review Article

The origin of pre-neoplastic metaplasia in the stomach: Chief cells emerge from the Mist

James R. Goldenring[a,b,*], *Ki Taek Nam*[a,b], *Jason C. Mills*[c]

[a]*Nashville Department of Veterans Affairs Medical Center, Nashville, TN, USA*
[b]*Departments of Surgery and Cell and Developmental Biology, Epithelial Biology Center, Vanderbilt University School of Medicine, Nashville, TN, USA*
[c]*Divison of Gastroenterology, Departments of Medicine, Pathology, and Developmental Biology, Washington University School of Medicine, St. Louis, MO, USA*

ARTICLE INFORMATION

Article Chronology:
Received 6 May 2011
Revised version received
23 August 2011
Accepted 24 August 2011
Available online 31 August 2011

Keywords:
Gastric adenocarcinoma
Metaplasia
SPEM
Intestinal metaplasia
Transdifferentiation
Chief cell
Zymogenic cell

ABSTRACT

The digestive-enzyme secreting, gastric epithelial chief (zymogenic) cell is remarkable and underappreciated. Here, we discuss how all available evidence suggests that mature chief cells in the adult, mammalian stomach are postmitotic, slowly turning over cells that arise via a relatively long-lived progenitor, the mucous neck cell, The differentiation of chief cells from neck cells does not involve cell division, and the neck cell has its own distinct pattern of gene expression and putative physiological function. Thus, the ontogeny of the normal chief cell lineage exemplifies transdifferentiation. Furthermore, under pathophysiogical loss of acid-secreting parietal cell, the chief cell lineage can itself trasndifferentiate into a mucous cell metaplasia designated Spasmolytic Polypeptide Expressing Metaplasia (SPEM). Especially in the presence of inflammation, this metaplastic lineage can regain proliferative capacity and, in humans may also further differentiate into intestinal metaplasia. The results indicate that gastric fundic lineages display remarkable plasticity in both physiological ontogeny and pathophysiological pre-neoplastic metaplasia.

Contents

* *Corresponding author at:* Vanderbilt University School of Medicine, Department of Surgery, Epithelial Biology Program, 10435G MRB IV, 2213 Garland Avenue, Nashville, TN 37232, USA. Fax: +1 615 343 1591.
E-mail address: jim.goldenring@vanderbilt.edu (J.R. Goldenring).

0014-4827/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.yexcr.2011.08.017

Introduction

Normal chief cell location and function

The gastric epithelium is organized as a series of roughly funnel-shaped invaginations from the gastric lumen known as gastric units. In the glandular portion of the stomach (known in most species as the corpus or body) each gastric unit is broadest where it adjoins the gastric lumen proper. This broad pit region is lined by simple columnar, mucus-secreting epithelium. Below the pit zone, the gastric unit narrows into one or multiple glandular branches. In mammals, proliferative activity and the presumptive stem cell are located where the pit narrows into each gland in a small region known as the isthmus [1,2]. The glands secrete both digestive enzymes and acid, a function that can be performed by a single oxyntico-peptic cell in birds [3,4], whereas in mammals, these functions are divided into two autonomous lineages: acid-secreting parietal cells and digestive-enzyme (zymogenic) producing chief cells. Even in mammals, parietal and chief cells likely develop from a common progenitor [5,6]. Chief cells occupy most of the base of a gastric gland, the upper ones organized as simple cuboido-columnar cells, the lower ones outpouching into an acinar configuration at the very base [7]. Parietal cells can occur throughout the gastric unit, but the vast majority are located in the neck of the gland, between the isthmus and the base [8,9].

Normal chief cell maturation requires XBP1 and MIST1

The chief cell is a large cell with an extensive network of lamellar rough endoplasmic reticulum (rER), concentrated around the basally oriented nucleus, and numerous, large, apical exocrine secretory granules filled with digestive enzymes. Recent studies have identified the transcription factors regulating this specialized cellular architecture. Conditional deletion of X-Box Binding Protein 1, XBP1, in mice leads to small chief cells with only scattered, scant rER [10], consistent with the known role of XBP1 in inducing cellular rER formation. XBP1 directly induces the basic Helix-Loop-Helix (bHLH) transcription factor MIST1 (Fig. 1). MIST1 (BHLHA15) is required for the basal localization of the nucleus and the maintenance of substantial apical cytoplasm filled with abundant, large vesicles [11]. Thus, chief cell structure is seemingly completely dependent on an XBP1 to MIST1 sequence, wherein XBP1 directly induces the extensive rER network (for translation of all the digestive enzymes), and MIST1 in turn regulates the

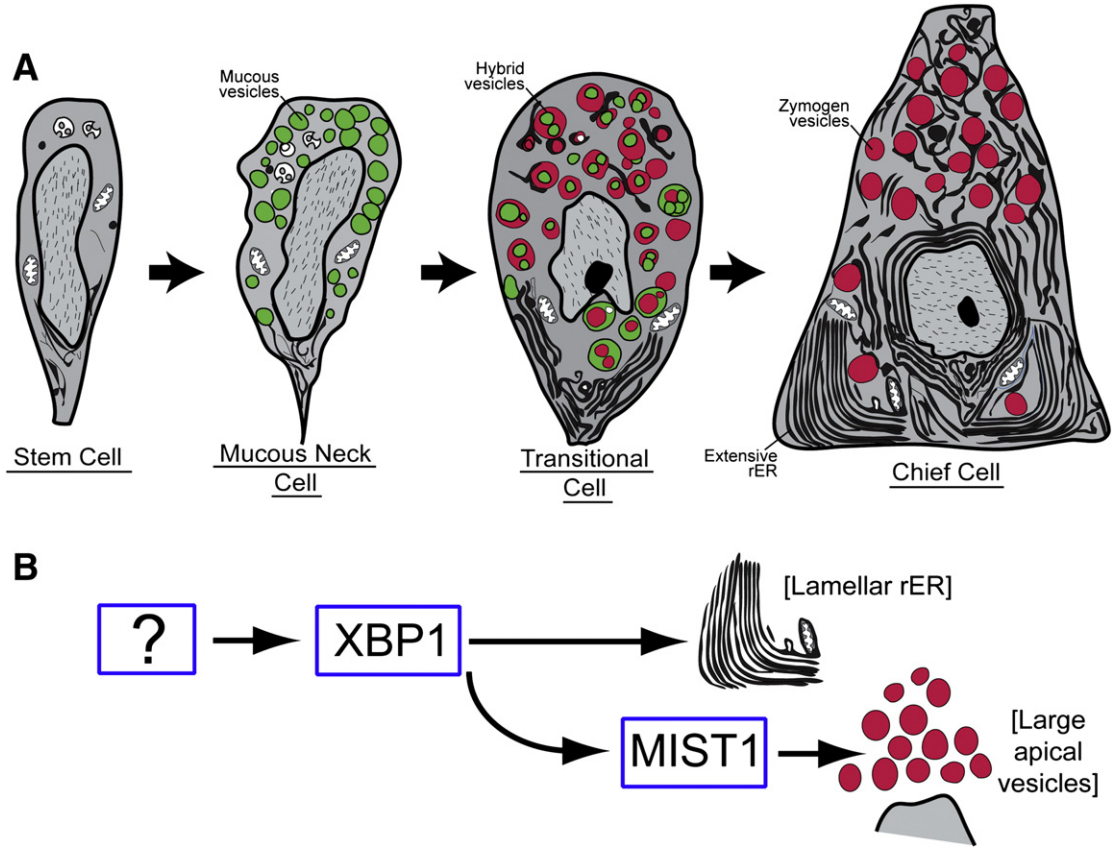


Fig. 1 – The cellular lineage ontogeny of normal gastric chief cells. A. Scheme for the origin of chief cell lineages from mucous neck cells. B. Transcription factor cascade responsible for maturation of normal chief cells.