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Invited review

Fibroblasts and myofibroblasts of the intestinal lamina propria in physiology and disease

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ABSTRACT

In this Review we summarize our current understanding of the biology of mesenchymal cells of the intestinal lamina propria focusing mainly on fibroblasts and myofibroblasts. The topics covered include 1) the embryonic origin of mesenchymal cells of the intestinal lamina propria and their heterogeneity in adults, 2) the role of the mesenchyme in intestinal development, 3) the physiological function of fibroblasts and myofibroblasts in adults as part of the intestinal stem cell niche and the mucosal immune system and 4) the involvement of fibroblasts and myofibroblasts in epithelial homeostasis upon injury and in the pathogenesis of diseases such as Inflammatory Bowel Diseases, fibrosis and cancer. We emphasize studies addressing the function of intestinal mesenchymal cells *in vivo*, and also discuss major open questions and current challenges in this field.

Contents

Abbreviations: α-SMA, α-smooth muscle actin; BMP, bone morphogenetic protein; Cox-2, cyclooxygenase-2; DSS, dextran sodium sulfate; ECM, extracellular matrix; EGF, epidermal growth factor; FGF, fibroblast growth factor; Foxf, forkhead box protein F; HGF, hepatocyte growth factor; IBD, inflammatory bowel diseases; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; MMP, matrix metalloproteinase; NLRP, NACHT, LRR and PYD domains-containing protein; PDGF, platelet-derived growth factor; PGE_2, prostaglandin E_2; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases; TNF, tumor necrosis factor; TNBS, trinitrobenzenesulfonic acid; TLR, toll-like receptor

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1. Introduction

The term "mesenchymal cells" of the intestinal lamina propria (i.e. the connective tissue between the epithelium and the muscularis mucosae), is used to collectively refer to non-hematopoietic, non-epithelial, non-endothelial cell types such as intestinal fibroblasts, myofibroblasts, pericytes, lymphatic lacteal smooth muscle cells, smooth muscle cells of the muscularis mucosae and mesenchymal stromal/stem cells (Powell et al., 2011). The biology of intestinal mesenchymal cells has witnessed significant progress during the last two decades, covered by a series of excellent reviews by Powell and colleagues (Mifflin et al., 2011; Pinchuk et al., 2010; Powell et al., 2005; Powell et al., 1999; Powell et al., 2011). Despite this progress, the origin, the heterogeneity and the role of intestinal mesenchymal cell types in physiology and disease remain poorly understood. Here, we summarize recent advances in the biology of fibroblasts and myofibroblasts of the intestinal lamina propria and also discuss emerging questions, open challenges and future directions in this field.

2. Architecture of the intestinal mesenchyme

The limited understanding of the structure and the function of the mesenchyme in the past is nicely reflected in the origin of this term, from the Greek words *mesos* (=intermediate) and *énchyma* (=infusion), used to define a loosely formed tissue filling the gap between other tissues of known function such as the epithelium and the smooth muscle. A series of electron microscopy studies performed in the '80s and '90s showed that the lamina propria mesenchyme has a layered architecture, characterized by the presence of specialized conformations of the extracellular matrix (ECM) and morphologically distinct fibroblast-like cells in each layer and along the crypt/villus axis (Fig. 1A) (Furuya and Furuya, 2007). Intestinal epithelial cells lie directly above a layer of ECM, the *basal lamina*, which is continuous in the crypts but discontinuous in the upper part of the villi where 0.5–5 μm in diameter pores, called *fenestrations*, are observed (Komuro, 1985). The basal lamina rests above a second layer wherein collagen fibrils and sub-epithelial fibroblasts form a reticular sheet with 3–7 μm in diameter pores juxtaposed to the fenestrations, the *foramina* (Fig. 1B) (Toyoda et al., 1997). The basal lamina together with the underlying reticular network is known as the *basement membrane* which lies above an extensive network of fibroblast-like cells. These fibroblasts form a basket-like network around the crypts that are tightly arranged in the lower part of the villi but their morphology changes towards the upper part of the villi where

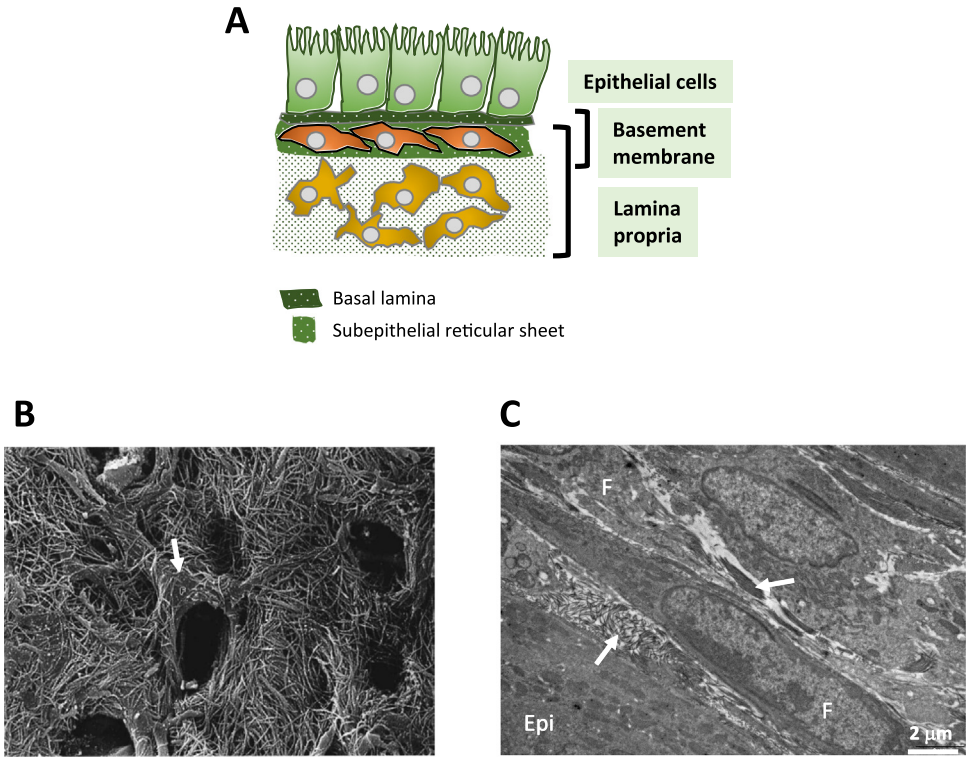

Fig. 1. Architecture of the intestinal mesenchyme. A. Intestinal epithelial cells are attached to the basement membrane which consists of the basal lamina and a reticular sheet including fibroblasts. The basement membrane lies above an extensive network of fibroblast-like cells located deeper in the lamina propria. B. Scanning electron microscopy observation of the rat jejunum mesenchyme after depletion of the epithelial layer and the basal lamina. Collagen fibrils and sub-epithelial fibroblasts (arrow) form a reticular sheet with 3–7 μm in diameter pores called foramina (Magnification 8800 ×). Adapted from Toyoda et al. (1997) with permission from S. Karger, AG, Basel. C. A transmission electron microscopy microphotograph of the sub-epithelial mesenchyme taken from a normal mouse colon specimen. Spindle-shaped fibroblasts (F) are located just under the epithelial layer (Epi), embedded in a dense network of collagen fibrils (arrows). A mesenchymal cell located deeper in the lamina propria is observed at the upper right part of the picture.