16 Growth Factors and Cytokines in Chronic Pancreatitis

S.K. Vyas

Introduction

The pathological appearances of chronic pancreatitis are characterised by parenchymal fibrosis, ductal stones and strictures, acinar cell atrophy and inflammatory infiltration by macrophages, neutrophils and lymphocytes. One of the key features of pancreatic fibrosis is an abundant presence of fibroblasts and an accumulation of a dense extracellular matrix which is rich in fibril-forming collagens type I and III. Deposition of extracellular matrix in a diseased pancreas must therefore be regarded as a wound-healing response, much as in fibrosis due to chronic injury in the lung, liver, kidney or joints.

In response to chronic injury, cytokines, growth factors and metabolites produced by resident and recruited cells in the pancreas may contribute to the disturbance of the physiological state. Such injury may produce changes in the amount and type of cells and in the qualitative and quantitative nature of the matrix components produced by these cells. Additionally, in response to chronic pancreatic injury, an increased number of endogenous non-parenchymal cells is seen histologically. This is in part due to the local proliferation of stromal fibroblasts but also due to the recruitment of new cells – leucocytes, macrophages/monocytes and lymphocytes – from the circulation, in response to chemotactic substances, growth factors and cytokines, with diverse effects on cell growth, differentiation, matrix synthesis and degradation. The relative importance of these inflammatory cells may vary between histological types of chronic pancreatitis. For example, increased abundance of lymphocytes is seen with immunohistochemical evidence for the class II major histocompatibility antigen HLA-DR, expressed in chronic obstructive and chronic calcifying but not in the diffuse fibrosing form of chronic pancreatitis (1).

This chapter will review the current literature on growth factors and cytokines which may be important in the pathogenesis of chronic pancreatitis. The bulk of our knowledge of the various important mediators of the wound-healing response is derived from studies of non-pancreatic tissues and inferences drawn from such studies need to be tested in pancreas-specific models; recent advances in maintaining different pancreatic cell types in primary culture and increasing evidence from transgenic studies have begun to facilitate this.
**Mechanism of Action of Growth Factors**

Growth factors and cytokines are small extracellular polypeptide molecules that bind to a target cell-surface receptor and trigger a response usually mediated via a signal transduction pathway. The cellular response may be altered differentiation or cell proliferation effected through the activation of specific gene expression. For a soluble protein to mediate an effect on a cell, it must first be in close proximity to that cell in a biologically active state while the target cell must be capable of responding to it (i.e. expressing specific receptors). A considerable complexity of cooperation between different mediators exists with discoordinate effects of individual cytokines on different tissues (see below).

A major emerging concept in pancreatic fibrogenesis is the modulation of cellular matrix synthesis and fibroblast proliferation. Some key growth factors have already been identified in pancreatic fibrosis and the evidence for their relevance in pancreatic fibrosis will be discussed. However, further studies of the cellular origin, effects on matrix turnover and regulation are required to understand their role in the pathogenesis of chronic pancreatitis.

**Growth Factors in Chronic Pancreatitis**

**Transforming Growth Factor-beta**

Transforming growth factor-beta (TGFβ) is a multifunctional protein capable of influencing cell proliferation, differentiation and a variety of cellular functions. This family of ubiquitous homodimeric 25-kDa cytokines (TGFβ 1–3) is secreted in latent, inactive forms that are not recognised by cellular receptors (2). When the molecule is latent, the precursor region remains dimerised; loss of this dimerisation leads to generation of the active species (3). Activity may be regulated by the isoform expressed, its rate of secretion and activation, its rate of release from the extracellular matrix or by the extent of receptor binding of active TGFβ.

In general, TGFβ stimulates growth of cells of mesenchymal origin, but inhibits growth of hepatocytes, epithelial cells, T and B lymphocytes. TGFβ has been shown to enhance the synthesis of extracellular matrix proteins including collagens, fibronectin and proteoglycans in many systems including the pancreas. In addition to stimulation of matrix synthesis, it also enhances fibrogenesis by inhibiting matrix degradation. TGFβ has been shown to decrease the synthesis of proteases (2,4) but the synthesis of protease inhibitors such as plasminogen activator inhibitor (5) and tissue inhibitors of metalloproteinases (TIMPs; see below) is down-regulated by TGFβ. TGFβ is expressed primarily in acinar and stromal cells of the intact pancreas (6). However, in pancreatic injury local expression and release of TGFβ is increased, predominantly in pancreatic ductal cells, islet cells and in vascular smooth muscle and endothelium (7). Overexpression of TGFβ-1 in murine pancreas induces massive fibrosis and diabetes (8) while repeated administration of recombinant TGFβ induces pancreatic fibrosis after repeated courses of acute pancreatitis (9). Transgenic TGFβ overexpression in the pancreas also leads to fibroblast proliferation, enhanced matrix deposition including fibronectin and laminin and induction of plasminogen activator