CHAPTER 9
Endothelin and the Airway Epithelium

Joaquim Mullol, James N. Baraniuk, Cesar Picado and James H. Shelhamer

1 Fundació Clinic per a la Recerca Biomèdica, Institut d’Investigacions Biomèdiques "August Pi i Sunyer", Hospital Clinic i Universitari, Barcelona, Catalonia, Spain
2 Division of Rheumatology, Allergy and Immunology, Department of Medicine, Georgetown University Medical Center, Washington DC, USA
3 Servei de Pneumologia i Alergia Respiratoria, Hospital Clinic i Universitari, Departament de Medicina, Universitat de Barcelona, Barcelona, Catalonia, Spain
4 Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

1. Introduction

The airway epithelium plays an important role in host defense as a barrier against physical, pathological and chemical stimuli. The epithelium is also an active metabolic and biosynthetic site for production and release of mediators, such as arachidonic acid metabolites, cytokines and a putative epithelium-derived relaxing factor, associated with the regulation of the bronchomotor tone and airway inflammation.

The role of endothelins (ETs) in the respiratory tract has been previously reviewed elsewhere [1–12]. ETs constitute a family of 21-amino acid
peptides originally isolated from the culture supernatant of porcine aortic endothelial cells [13]. ET has potent vasoconstrictor [14-15], bronchoconstrictor [15] and glandular secretory effects [16-18]. ET has at least three genomic isoforms, ET-1, ET-2 and ET-3 [19], which act through to at least two different receptors, ET_A and ET_B [20-22]. ET-1 and ET-2 bind to ET_A receptors more avidly than ET-3, whereas all three bind to ET_B receptors with equal affinity.

2. Endothelin Synthesis and Release

Endothelin may be also produced by non-endothelial cells such as epithelial cells. ET production by airway epithelial cells likely exerts both paracrine and autocrine effects.

2.1. Lower Airway Epithelium

2.1.1. Animal Studies: Immunoreactivity to endothelin (irET-1 and irET-3) is detected in conditioned culture medium from both canine and porcine tracheal epithelial cells [23]. IrET is present in ciliated and secretory bronchiolar epithelial cells in Wistar rats and mice [24]. In the cultured and intact epithelium from rabbit trachea, irET-1 is found, together with SP and arginine-vasopressin [25]. In piglet lung, focal irET-1 is seen over epithelial cells of bronchi, bronchioles and terminal bronchioles [26], raising the possibility that ET-1 could play a role in the regulation of bronchial, as well as vascular, tone and development. In the guinea-pig, the non-ciliated epithelial (Clara) cells are also a source of ET-1, but not ET-2 and ET-3 [27,28]. In guinea-pig tracheal epithelial cells, ET-1 content of the submucosal side is over 30 times higher than that of the apical side, suggesting the release of ET-1 from airway epithelial cells toward the submucosal side [29]. Bronchiolar epithelial cells from fetal and adult rat lungs express ET mRNA [30].

Several stimuli may induce ET production from epithelial cells. Isolated epithelial cells from rabbit trachea selectively released ET in response to thrombin in a mechanism dependent on protein synthesis and connected with activation of phospholipase C [31]. However, in piglet lung, no changes in the distribution of ET-1 in airway epithelium were observed after exposure to several stimuli such as hypoxia and α-thrombin [26].

Bacterial lipopolysaccharide (LPS) endotoxin is known to produce airway epithelial damage and airway hyperreactivity in guinea pigs. The increase in ET-1 [32] and ET-1 mRNA [33] induced by bacterial endotoxin in cultured epithelial cells may be related to this hyperreactivity. In guinea pig cultured tracheal epithelial cells, cytokines involved in damage, inflam-