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Epithelial Cells Interaction-Review Paper

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INTRODUCTION

Airways are exposed to a number of inhaled toxins, pathogens, allergens, reactive gases, aerosols and irritant particles. After a lung insult, some of the epithelial cells are injured or damaged. These cells either detach or die thus disruption of cell-cell and cell-matrix interaction and also exposing the basement membrane. The normal response to the injury is a mass transportation of factors including Extra Cellular Matrix (ECM), various growth factors and inflammatory cells. The epithelial cells in the margin of the damage flatten and move to eventually cover the wound[1,2]. If this repair does not occur this insult can result in a disease (Fig. 1).

So far there are little data showing which cell types are involved and by what mechanism this repair takes place. There are two main hypothesis how the repair might take place. The first model postulates that basal cells act as the principal stem cell in the conducting airways, giving rise to the various secretory cells and ciliated cells. This model is based on the cell turnover studies of normal respiratory epithelium[2]. The other model postulates that the secretory cells are the progenitor cells from which most of the other cells develop. The evidence on this second model is based from the regeneration of chemically or physically injured epithelium[2].

The most common basally situated cell, the 'basal' cell was described and proposed as a progenitor cell[3]. In peripheral bronchioles where basal cells are absent, the Clara cell is the progenitor cell[4]. Clara cells may divide in response to epithelial irritation and subsequently differentiate to form mature secretory and ciliated cells[5]. In the alveolus, the type II cell is the progenitor cell from which the type I cell differentiate[6]. Thus epithelial cells interactions play an important role in the repair mechamism.

Cell interactions: Cell interactions are an important factor for the maintenance of both three-dimensional structure and normal function in tissues. The biochemical entities mediating cell adhesion are multiprotein complexes comprising three broad classes of macromolecules: the adhesion receptors, the extracellular matrix molecules and the adhesion plaque proteins[7].

The extracellular matrix has been traditionally viewed as either forming the structurally stable support for cells and tissues or as being responsible for the basement membrane formation[8]. It is known that extracellular matrix-cell interactions regulate the morphology and cell functions through a family of specific cell surface receptors-the integrins[9-11].

Cell adhesion receptors are typically transmembrane glycoproteins that mediate binding to Extra Cellular Matrix (ECM) molecules or to counter-receptors on other cells. These molecules determine the specificity of cell-cell and cell-ECM interactions. The ECM proteins are usually fibrillar in nature and provide a complex structural and functional nature that can interact simultaneously with multiple cell surface receptors. The peripheral membrane proteins provide structural and functional linkages between adhesion receptors and the actin microfilaments, microtubules and intermediate filaments of the cytoskeleton[12,13].

Extra cellular matrix (ECM): Extra cellular matrix (ECM) is a general term that encompasses components of the basement membrane and interstitial connective tissue. The extracellular matrix contains signals that control cell shape, migration, proliferation, differentiation, morphogenesis and survival[9,10]. The basement membrane comprises collagen IV, laminins, entactin, fibronectin and proteoglycans while the interstitial connective tissue is made of fibrillar collagens, elastic fibers and proteoglycans[14,15]. Interstitial connective tissue is important during development and wound repair[14,15].

ECMs act in concert with other signalling pathways, such as those initiated by growth factors, to regulate cell behaviour[11]. Cells use a series of receptors for ECM including integrins[16], cell surface proteoglycans[17,18] and cell-surface-expressed tyrosine kinase receptors with direct affinity for ECM[19,20]. The components of ECM include insoluble ECM proteins such as collagens,

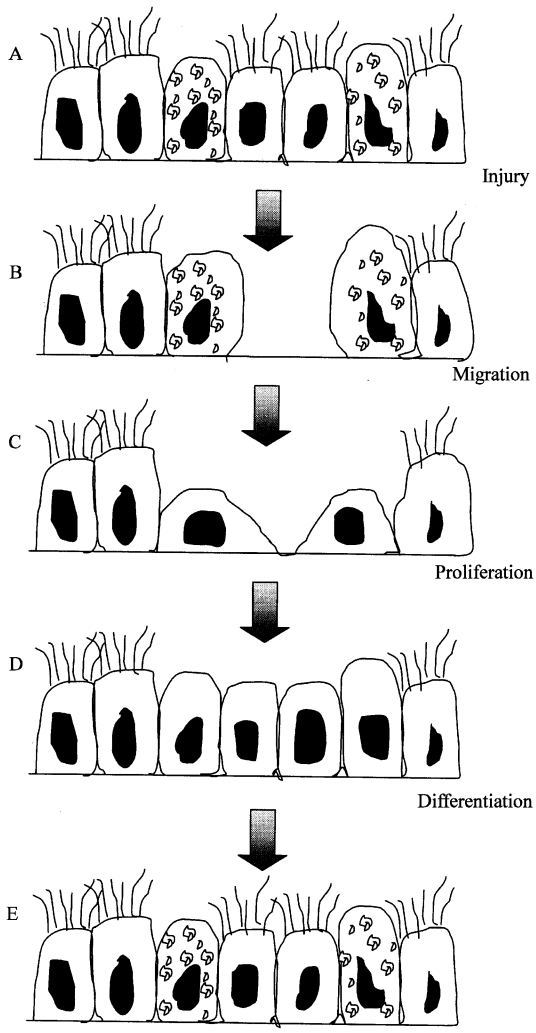

Fig. 1: Stages of injury and repair in lung bronchiolar region (A) Normal epithelium (B) After an injury portions of basement membrane is de-nuded (C) provisional matrix is deposited and neighbouring cells migrate to fill up the gaps in the epithelium (D) Progenitor cells proliferate and (E) cells differentiate in order to restore the epithelium

laminins, fibronectin and proteoglycans, matricellular ECM proteins that modulate cell-matrix interactions and other cellular responses such as cell proliferation and ECM-associated proteins such as growth factors[9-11].

During tissue injury, the composition of ECM and its cellular recognition sites are altered in a number of significant ways. Increased vascular permeability results in recruitment of plasma-derived proteins including fibronectin, vitronectin and fibrinogen into the ECM, whereas cells in the injury site are induced to release or synthesise new components including thrombospondins, tenascins and alternatively spliced fibronectins which regulate tissue repair[21,22]. Furthermore, tissue injury may result in alterations in existing ECM proteins within tissues or in recruited ECM that reveal cryptic biologically active sites (matricryptic) that provide important signals within the injury sites[23,24].

Among the extracellular matrix proteins, fibronectin matrices appear critical to tissue repair. Following tissue injury, the expression of fibronectin increase dramatically[25]. Much of the fibronectin detected in injured lungs is of plasma origin, but it is also locally synthesised by macrophages, fibroblasts, endothelial cells and surface epithelial cells [22,23]. Fibronectin may serve multiple functions in tissue repair, acting as a chemo-attractant and adhesive substrate for mesenchymal and epithelial cells, which migrate into damaged tissue[26]. In addition to fibronectin, two components of the basement membrane, laminin and type IV collagen, can stimulate bronchiole epithelial cell migration[20,27].

Integrins: The integrins are a family of cell-surface glycoproteins that act as receptors for ECM proteins or for membrane-bound counter-receptors on other cells[1628]. Integrins mediating cell-ECM adhesion sites are complex specialised structures termed focal contacts or focal adhesions[29]. Each integrin is a heterodimer that contains an α and a β subunit, each subunit having a large extracellular domain, a single membrane-spanning region and in most cases (other than β_4), a short cytoplasmic domain[16,30].

The integrin receptor family of vertebrates include at least 16 distinct α subunits and 8 or more β subunits which can associate to form more than 20 distinct integrins[31]. The α/β pairings specify the ligand-binding abilities of the integrins heterodimers. Although the ligands for integrins are often large ECM proteins such as collagen, laminin, vitronectin, or fibronectin, some integrins recognise rather short peptide sequences within the larger proteins, for example, the RGD (Arg-Gly-Asp) sequence found in the fibronectin and vitronectin. In other studies, however, integrin-ligand recognition depends on the overall conformation of the ligand protein. For example, some integrins interact with members of other adhesion receptor families, including Ig-Cams and cadherins, in a manner that does not involve RGD motifs[32]. Some integrins such as $\alpha_5\beta_1$ bind to a single ECM protein in this study fibronectin[25], while other integrins such as $\alpha_v\beta_3$ has been reported to bind to vitronectin, fibrinogen, von Willebrand factor, thrombospondin, fibronectin, osteoporotin and collagen[16,30,34] (Table 1).

Cells often display multiple integrins capable of interacting with a particular ECM protein, thus integrin

Table 1: The integrin receptor family and putative ligands. (Hynes,[31]; Kumar,[32]; Damsky and Werb,[32]; Fornaro and Languino,[34]; Sheppard,[36]; van der Flier and Sonnenberg,[16])

	Subunits	Ligands and counter-receptors
β_1	α_1	Collagens, laminin, fibronectin
	α_2	Collagens, laminin
	α_3	Collagens, laminin, fibronectin
	α_4	Fibronectin, VCAM-1
	α_5	Fibronectin
	α_6	Laminin
	α_7	Laminin
	α_8	Fibronectin, tenescin
	α_9	Vitronectin, fibronectin
	α_{10}	Collagen
	α_{11}	Collagen
β_2	α_L	ICAM-1, ICAM-2
	α_M	ICAM-1, fibrinogen, factor X
	α_X	Fibrinogen
β_3	α_{IIb}	Fibrinogen, fibronectin, von willebrand factor, vitronectin, thrombospondin
	α_v	Vitronectin, fibrinogen, von willebrand factor, thrombospondin, fibronectin, osteoporotin, collagen
β_4	α_6	Laminin
β_5	α_v	Vitronectin
β_6	α_v	Fibronectin
β_7	α_4	Fibronectin, VCAM-1
	α_E	?
β_8	α_v	?

Table 2: Intracellular proteins suggested to interact with integrin subunit cytoplasmic domains. (Hemler,[40]; Dedhar and Hannigan,[41])

Proteins	Integrin subunit(s)	
Cytoskeletal		
Proteins	α-actinin	β_1, β_2, β_3
	Talin	β_1, β_2, β_3
	Filamin	β_2
	Tensin, vinculin, paxillin, actin	β_1
	F-actin	α_2
Regulatory and signal transducing proteins	Endonexin	β_3
	Calreticulin	α_2, α_3, α_4, α_v, α_6
	IAP	α_v
	CD9, CD63	$\alpha_3\beta_1$
	FAK	β_1, β_2, β_3
	ILK	β_1, β_2, β_3
	IRS-1	$\alpha_v\beta_3$
	p-190	$\alpha_v\beta_3$
Other signalling molecules	C-CSK, P13K, Rho, Ras, Grb2, MEKK, MEK, ERK1, ERK2, CAS, Src family kinases	?

expression is often apparently redundant, at least in terms of simple cell adhesion. Some integrin subunits undergo alternative splicing of their cytoplasmic domain regions in a tissue-type specific and developmentally regulated manner, which suggests that there are discrete intracellular functions for individual integrins[34].

The integrin cytoplasmic domains determine the interactions between the extracellular environment, intracellular structure and cascades signalling. Both the α and β subunit cytoplasmic domains make important contributions to various aspects of overall integrin function including cytoskeletal organisation, cell motility, signal transduction and modulation of integrin affinity for ligands[16,37].

The α subunit cytoplasmic domain inhibits certain functions of the β cytoplasmic domain (eg, the focal contact recruitment) but the binding of a ligand to the integrin relieves this inhibition, possibly by allowing the subunits to swing apart like a hinge. The β cytoplasmic domain is also important in signal transduction, particularly integrin activation of FAK, whereas the truncation/mutation of the α cytoplasmic domain has little effect on this process[38,39].

Several cytoplasmic proteins including talin, α-actinin and possibly Focal Adhesion Kinase (FAK) bind directly to the β_1 cytoplasmic domain and contribute to integrin-cytoskeletal interactions and bidirectional transmembrane signalling[13,34]. Table 2 summarises the various intracellular proteins that interact with integrin subunit cytoplasmic domains.

Integrins activate a number of a large array of signalling intermediates. Their effects include activation of Rho-family GTP-ases leading to changes in cytoskeletal organisation, activation of Mitogen-Activated Protein (MAP) kinase pathways and activation of an array of proteins and lipid kinases. These signalling pathways allow integrins to influence cell-cycle progression, cell survival and gene expression in addition to their effect on

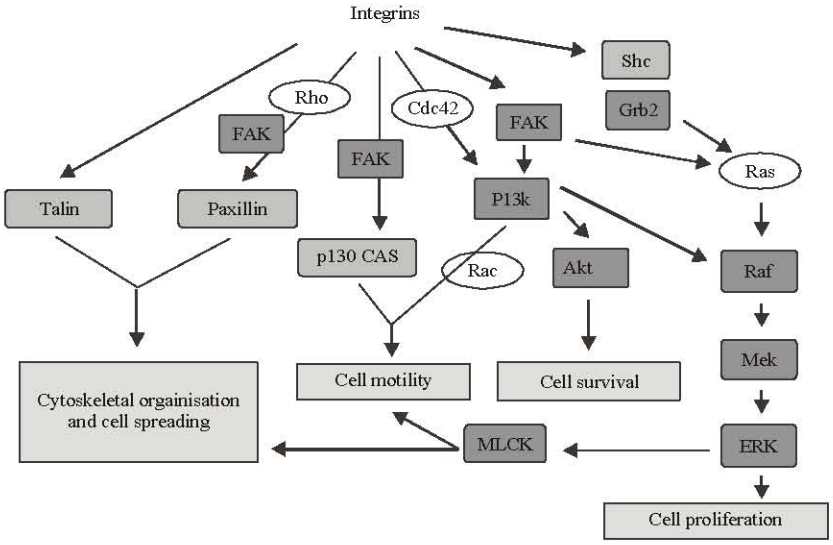

Fig. 2: Summary of the integrin signalling intermediates, including small GTPases (blue), protein kinases (red) cytoskeletal proteins (orange) and others. Integrins can affect many biological processes (yellow). Adapted from Hynes[3]

cell adhesion and morphology[16,42,43]. In fact, most cells will not proliferate or survive unless they are adhering to a substrate-so called anchorage dependence[16,44].

Various biological responses are affected by integrins, including cytoskeletal organisation and cell spreading[16,44], cell motility [45,46], cell survival [37] and cell proliferation[16,47]. A simplified pathway showing the signalling mediated adhesion receptors and signalling intermediates is shown in Fig. 2.

Cadherins: Cadherins comprise a family of transmembrane proteins that share an extracellular domain consisting of multiple repeats of a cadherin-specific motif[48]. The classical subfamily is calcium dependent homotypic cell-cell adhesion molecules. Several members which fall in this subfamily have been characterised including N-, P-, R-, B- and E-cadherin as well as approximately 10 others[49]. These molecules are present in specialised sites of cell-to-cell adhesion (termed adherence junction), whereby they can establish linkages with the actin-containing cytoskeleton known as adhesion zippers[13]. The classical cadherins play a key role in developmental processes[50,51].

Another important subfamily of cadherins involved in the adhesion is represented by the desmogleins and desmocollins, a group of desmosome-associated cadherins that form intracellular linkages to intermediate filaments rather than actin filaments[52].

The cytoplasmic domains of cadherins interact strongly with a group of intracellular proteins known as catenins. It was shown that catenins are essential for cadherin function. Truncation of the cadherin cytoplasmic domain to delete catenin binding sites lead to a loss of cadherin-mediated adhesion[7,50]. Due to the fact that different classic cadherins have considerable homology among their cytoplasmic domains, they compete for the same catenins[53]. Three forms of catenin proteins have been described, α-, β- and ã-catenin. The structure of α-catenin shows substantial homology to the protein vinculin, which binds α-actinin and talin and is critical for cytoskeletal assembly at integrin-mediated focal adhesion sites[54]. β-catenin binds directly to the cadherin cytoplasmic domain, subsequently, α-catenin binds to β-catenin and links the complex to the actin cytoskeleton by direct interaction with actin and by binding α-actinin[52]. β-catenin does not only interacts with cadherins but also with components of the wingless/Wnt signalling pathway and thus can stimulate transcription of target gene[55,56] (Fig. 3).

Immunoglobulin-cell adhesion molecules (Ig-CAMs): Immunoglobulin superfamily cell adhesion molecules (Ig-CAMs) are defined by the presence of one or more copies of the Ig fold, a compact structure with two cysteine residues separated by 55 to 75 amino acids arranged as two anti-parallel β sheets[57]. In many studies, Ig-CAMs contain one or more copies of a fibronectin type III repeat domain[13].

Some examples of the Ig-CAMs superfamily include: Neural Cell Adhesion Molecules (NCAM)[58,59], EpH[59],

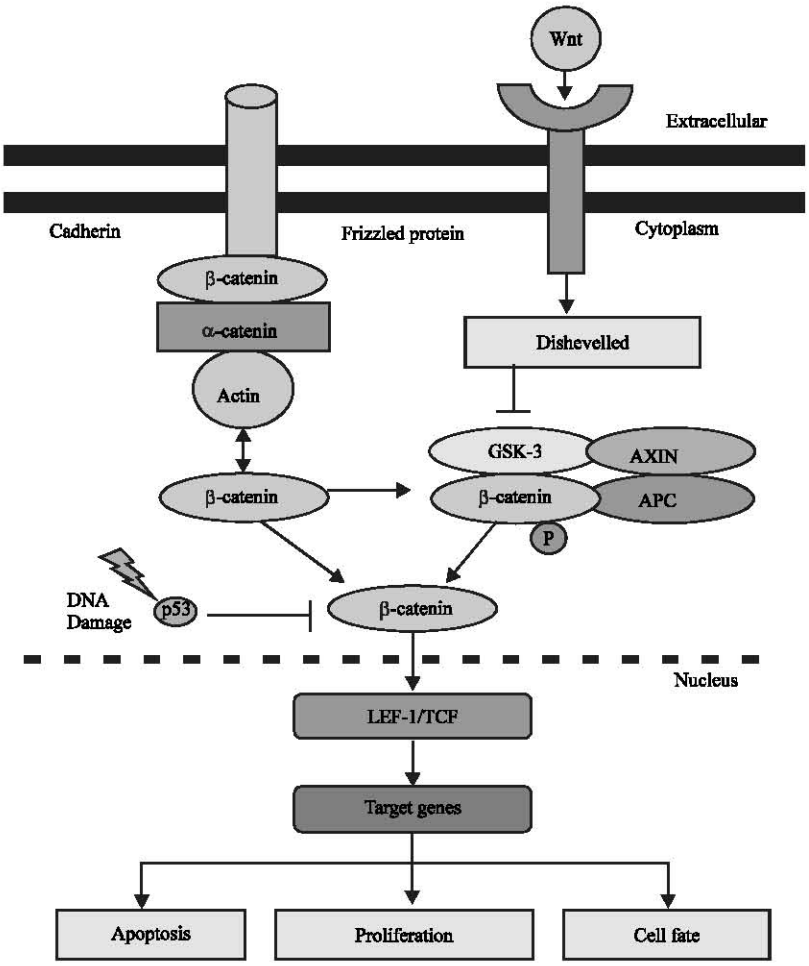

Fig. 3: Schematic presentation of the Wnt/β-catenin pathway. In absence of a mitotic signal, β-catenin is sequestered in a complex with adenomatous polyposis coli (APC), glycogen synthetase kinase (GSK-3) and scaffolding protein axin and is phosphorylated by GSK-3, enabling its degradation. An activation of Wnt pathway leads to activation of dishevelled (Dsh) protein which downregulates the complex so that it no longer phosphorylates β-catenin. The increased level of free β-catenin translocates to the nucleus, bind to transcription factors (LEF-1/Tcf) and stimulate ranscription of target gene. Free β-catenin can be inhibited by p53. (Aplin *et al.*,[13]; Bremnes *et al.*,[56]; Moon *et al.*,[63]

CD2, CD4, CD8[60], intercellular adhesion molecule 1 and 2, (ICAM-1, ICAM-2)[60,61], T-Cell Receptor (TCR) [60-62] lysophosphatidic acid (LFA-3)[13], vascular cell adhesion molecule-1 (VCAM-1)[13], platelet endothelial cell adhesion molecule-1 (PECAM-1) (DeLessier *et al.*, 1994), Receptor Protein Tyrosine Phosphatases (RPTPs) and others.

Ig-CAMs play multiple roles in the developing embryo and in the adult organisms. They are important in tissue organisation and cellular trafficking in the immune system[13].

Selectins: Selectins are a small family of lectin-like adhesion receptors composed of three members, L-, E- and P-selectin[64,65]. The structure of a selectin includes an amino-terminal domain that is homologous to calcium-dependent animal lectins, followed by an epidermal growth factor (EGF)-type domain, two to nine complement regulatory protein repeats, a transmembrane helical segment and a short cytoplasmic tail[13]. Selectins mediate heterotypic cell-cell interactions through calcium-dependent recognition of sialyated glycans. The physiological role of selectins concerns leukocyte adherence to endothelial cells and platelets during inflammatory processes[60,61].

P-selectin is present in latent form in endothelial cells and platelets and it is rapidly translocated from secretory granules to the cell surface upon activation by thrombin

or other agonists[64,65]. P-selectin was found to be upregulated in bleomycin induced injury in rats and this was associated with neutrophil recruitment in response to bleomycin[66]. E-selectin is synthesised and expressed on endothelial cells in response to inflammatory cytokines such as Tumour Necrosis Factor (TNF) or interleukin-1 (IL-1)[64,65,67]. L-selectin is expressed constitutively on leukocytes, but its presentation at the cell surface may be regulated[64,65,67]. The precise identities of the ligands for the three currently known selectins are still not clear and are a matter of some controversy[68].

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