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Cell-Cell Interactions and Cross Talk Described in Normal and Disease Conditions: Morphological Approach

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1. Introduction

The contact between cells and their microenvironment is fundamental both during development and for the preservation of tissue structure. Picking out the signals coming from the surrounding environment enable cells to react promptly to changes that may occur. Various molecular mechanisms explain the ability of cells to sense the microenvironment could be grouped into two major classes: (1) the transmission of signals in the form of soluble molecules which interact with cellular receptors, such as growth factors, cytokines, hormones, etc., and (2) the interaction of cells with structural components of their environment, namely other cells and the extracellular matrix (ECM) [1].

Cell-cell interactions are central to the function of many organ systems. A common theme for heterotypic cell interactions is the interaction of parenchymal cells with nonparenchymal neighbors with resultant modulation of cell growth, migration, and/or differentiation. Specifically, these interactions are of fundamental importance in physiology [2, 3], pathophysiology [4, 5], cancer [6, 7] developmental biology [8, 9], wound healing [10, 11], and attempts to replace tissue function through 'tissueengineering' [12, 13]. Further understanding of how cell-cell interactions modulate tissue function will allow us to gain fundamental biological insight as well as suggest approaches that will allow the manipulation of tissue function in vitro for therapeutic applications in vitro for therapeutic applications [14].

2. Cell-cell interaction and cross talk phenomena during embryonic period

Cells are the true miracle of evolution. Once the basic building block, the eukaryotic cell, became available, the form of metazoans evolved by changing the arrangement of cells with respect to each other. Cell-cell interaction in embryo was described in literature to have a

vital role in cell differentiation and fate of developing cells, a process generally referred to as embryonic induction [15-17].

Jessell and Meltont [18] in their studies on the diffusible Factors in Vertebrate Embryonic Induction reported that one group of cells control the fate of neighboring cells. Inductive interactions involve two primary components. He added that the process involves a signal that is generated by the inducing cell and a receptive system that directly or indirectly controls gene expression in the responding cell. The competence of cells to respond to the ligand also contributes to the extent of induction. A good example of cellular interaction reported in this article is the induction of mesodermal development. In *Xenopus* blastula, vegetal blastomeric release extracellular signals that induce adjacent animal ectoderm (animal cap cells) to develop into mesodermal tissue such as muscles or mesothelia [19-21].

Inductive interactions involve two primary components: a signal that is generated by the inducing cell and a receptive system that directly or indirectly controls gene expression in the responding cell. The ligands that constitute inductive signals can be anchored to the cell surface or secreted from cells. Thus, the extent of induction can be controlled by regulating ligand production or by limiting its range of action. The competence of cells to respond to the ligand also contributes to the extent of induction. Competence may be controlled by modifying the expression or function of the appropriate receptors, the intracellular signal transduction pathway, or the transcription of target genes (Figure 1). Inductive signals can also control multicellular pattern if the response of similar cells to different concentrations of the same signal results in different cell fates [18].

Schmidt et al. [22] reported that Signals originating from embryonic ectoderm have a role in the development of underlying somites and neural crest which is mediated by Wnt family of secreted signaling molecules that controls a wide range of developmental processes in all metazoans. Neural crest is a population of multipotent progenitor cells that arise from the neural ectoderm in all vertebrate embryos and form a multitude of derivatives including the peripheral sensory neurons, the enteric nervous system, Schwann cells, pigment cells and parts of the craniofacial skeleton. Schmidt et al. [22] reported that neural crest induction requires an ectodermal signal. Signaling molecules of the Wnt, BMP, and FGF families and their downstream effectors have been shown to mediate neural crest induction [23-24].

Dorsolateral bending of the neural plate, an undifferentiated pseudo-stratified epithelium, is essential for neural tube closure which if failed spina bifida results. Ybot-Gonzalez et al. [25] pointed to the cellular interaction between neural crest cells and overlying neuroectoderm via molecular signaling that regulate the formation of dorsolateral hinge points (DLHPs) via antagonism of Bmp signaling that underlies the regulation of DLHP formation during mouse spinal neural tube closure.

3. Cellular interaction in nervous system

Glial cells are widely distributed throughout the nervous system. They have been found to have an impact on chemical synaptic transmission. Interplay among Schwann cells, the

nerve and the muscle will provide insights into a better understanding of mechanisms underlying neuromuscular synapse formation and function.

Feng and Ko [26] reported that perisynaptic Schwann cells (PSCs), which are the glia juxtaposed to the nerve terminal at the neuromuscular junction (NMJ) play active and essential roles in synaptic function, maintenance, and development. The authors also mentioned that PSCs can respond to nerve activity by increasing intracellular calcium and are capable of modulating synaptic function in response to pharmacological manipulations. Schwann cell-derived factors can also promote synaptogenesis and enhance synaptic transmission in tissue culture

Feng and Ko [27] had studied the role of glial cells in the formation and maintenance of the neuromuscular junction. The authors reported that during development, PSCs grow beyond nerve terminals and guide nerve terminal extension. Nerve terminals retract or stop extension after PSC ablation by complement-mediated lysis *in vivo*, suggesting that PSCs can promote synaptic growth and maintenance at developing NMJs.

Schwann cell-conditioned medium (SC-CM), with culture medium consisting of 45% Leibovitz's L-15 medium (Invitrogen), 45% Ringer's solution (in mM: 115 NaCl, 2 CaCl₂, 2.5 KCl, and 10 HEPES; pH 7.4), and 10% fetal calf serum (Invitrogen), which may be mediated by transforming growth factor-beta1, can promote synapse formation in *Xenopus* nerve-muscle culture. In addition, SC-CM contains small molecules (within 500-5000 Da), which can enhance spontaneous synaptic activities acutely and potently at developing frog NMJs. In adult muscles, PSCs can detect evoked synaptic activities and are capable of modulating transmitter release. Nerve terminals retract and synaptic efficacy is reduced at 1 week, but not within the first few hours, after PSC ablation. Thus, PSCs are essential for the long-term, but not short-term, maintenance of synaptic structure and function at the adult NMJ. After nerve injury, adult PSCs sprout extensive processes, which guide regenerating nerve terminals. Schwann cells express agrin and neuregulins, which may help the postsynaptic differentiation and synaptic repair. Furthermore, neuregulin-ErbB signaling pathways play an essential role in synapse-glial interactions at the NMJ. These recent findings suggest that PSCs play multiple roles and actively participate in synaptic development, modulation, maintenance, and repair of the vertebrate NMJ [27].

It was found that PSC interaction with nerve terminals play an important role in re-innervations at frog NMJs: regenerating NTs induce PSCs to sprout, and PSC sprouts, in turn, lead and guide the elaboration of NTs. After nerve injury, PSCs sprout profusely and PSC processes guide regenerating nerve terminals [26, 28].

4. Brain pericytes implication in blood brain barrier and pathological disorders

Brain microvascular pericytes are important constituents of the neurovascular unit. These cells are physically the closest cells to the microvascular endothelial cells in brain capillaries. They significantly contribute to the induction and maintenance of the barrier functions of

the blood-brain barriers [29]. The highest pericyte coverage around microvessels is found in the central nervous system (CNS). It is not clear why the CNS needs higher vascular pericyte coverage than other organs, but one of the possibilities is that pericytes contribute to the formation of the blood–brain barrier.

Brain pericytes was suggested in early studies to be as a source of macrophage activity. Results substantiate this functional role via success demonstration of macrophage markers, phagocytosis and antigen presentation. Coupled with current knowledge on the entry of lymphoblasts into brain tissue and perivascular areas as potentially being the primary site of cellular interactions for production of immune responses, this places the pericytes in a position to significantly contribute to central nervous system (CNS) immune mechanisms.

However, it has been shown from some studies with rat bone marrow chimeras that lymphocytes do normally enter CNS tissue [30]. It appears that only immature lymphocytes or lymphoblasts can gain access and they stay there 1 to 2 days [31]; this seems to be a continuous process though, which would mean the constant presence of a lymphoblast population. The immature nature of the cells probably explains why they were not previously detected. These lymphoblasts could then mature, become activated and participate in an immune response.

Other functions of pericytes in brain are controlling of blood flow, regulation of vascular development and immune responses [32].

5. Vascular cell-cell interactions through junctions

The vascular system is considered an excellent example that demonstrates cell adhesion and its regulation. Endothelial cell adhesion plays an essential role in the vascular response to pathological conditions, such as inflammation, ischemia wound healing and, in particular, cancer. Certainly, tumor-associated angiogenesis is key to cancer progression and metastasis, and vascular adhesion molecules are undoubtedly major players in this context [1].

It has become clear that vascular intercellular adhesion exhibits cell type-specific features that account for the specialized roles of the adhesive junctions in the endothelium [1].

In endothelial cells, tight junctions being often intermingled with adherens junctions along the intercellular boundaries rendering this junctional organization not as rigid. Adding together, endothelial cells do not contain desmosomes, although some desmosomal components are found in the complex adherens, a junctional structure specific to certain specialized vascular districts, such as a subset of lymphatic vessels and of veins [33].

The main difference between epithelial and endothelial AJs is that the latter do not contain E-cadherin but an endothelial-specific cadherin, called vascular endothelial (VE) cadherin. The expression of VE-cadherin is essentially restricted to cells of the endothelial lineage and starts very early during the differentiation of endothelial cell precursors [34].

Although VE-cadherin is found in all endothelial cell types, its levels vary in different vascular districts and during angiogenesis, including tumor vascularization. Indeed, the expression of VE-cadherin is enhanced in activated, cancer-associated vessels, suggesting a causal involvement in tumor angiogenesis [35].

Experimental evidence *in vivo* as well as in endothelial cell cultures pointed to an interplay between VE-cadherin-mediated adhesion and endothelial cell survival (i.e., resistance to programmed cell death or apoptosis). The molecular basis of this cross-talk probably lies in the ability of VE-cadherin to activate the phosphatidyl inositol-3 kinase (PI3K) pathway, an enzymatic cascade that ultimately leads to the inhibition of apoptosis [36].

Vascular Tight Junctions: Junctional adhesion molecules (JAMs) form a group of transmembrane proteins belonging to the immunoglobulin (Ig) superfamily, due to the presence of two Ig domains in their extracellular portion. JAMs appear to be associated with TJs rather than being integral components. As suggested by their name, a prominent feature of JAMs is their ability to promote intercellular adhesion via homophilic binding [37]. However, it is not clear to what extent the pro-adhesive function of JAMs is relevant *in vivo*.

The JAM family appears to play an important role in the recruitment of various proteins to the TJs. Indeed, JAM-A associates with zonula occludens-1 (ZO-1), cingulin, and occludin, inducing their localization at TJs (Figure 1) [38].

Figure 1. Vascular tight junctions. The molecular organization of the tight junction between endothelial cells is illustrated in a schematic manner, together with the non-junctional adhesion provided by PECAM-1 and CD146. Quoted from Cavallaro [1].

Recent observations have raised the possibility that JAMs are involved in tumor angiogenesis. Indeed, an antibody against JAM-C was reported to interfere with cancer growth by preventing neovascularization [39]. A major function of JAM proteins is their ability to regulate the trafficking of leukocytes and dendritic cells across the endothelium, a process that has crucial implications for the inflammatory response. Interfering with JAM function in vivo, e.g., by using neutralizing antibodies, blocks the transendothelial migration of monocytes and neutrophils in experimental models of inflammation. Vascular JAMs facilitate leukocyte endothelium interactions by heterophilic binding to blood cell integrins [40].

Some adhesion molecules expressed in endothelial cells do not show a specific association to junctional complexes. Platelet-endothelial cell adhesion molecule-1 (PECAM-1, also known as CD31) mediates inter-endothelial adhesion through homophilic binding. In addition, PECAM-1 has been implicated in a broad spectrum of vascular processes, including endothelial cell migration, survival, remodeling and angiogenesis [41].

Endothelial molecules, such as JAMs, PECAM-1 and CD146, that are involved in inflammatory infiltration could also facilitate the trafficking of tumor cells across the vascular wall. Hence, the therapeutic inhibition of adhesion molecules promoting transendothelial migration of inflammatory cells could prove useful also as a strategy to repress the metastatic dissemination of tumor cells [1].

Endothelial/Pericyte Interactions: Pericytes is the term for vascular mural cells embedded within the vascular basement membrane of blood microvessels, where they make specific focal contacts with the endothelium [42].

Morphologically, the pericytes exhibit a small, oval cell body with multiple processes extending for some distance along the vessel axis; these primary processes then give rise to orthogonal secondary branches which encircle the vascular wall. The contour of the cells conforms to that of the adjacent vascular element; also, they are usually enclosed within the basal lamina of the microvasculature [1].

Pericytes are now coming into focus as important regulators of angiogenesis and blood vessel function. Genetic data demonstrate the critical importance of pericytes for vascular morphogenesis and function, and imply specific roles for the cell type in various aspects of angiogenesis [43].

Development of a vascular system involves the assembly of two principal cell types - endothelial cells and vascular smooth muscle cells/pericytes (vSMC/PC) - into many different types of blood vessels. Senger and Davis [44] stated that Pericyte coverage leads to vessel remodeling, maturation and stabilization.

Pericyte-endothelial interaction mediated by cytokines: Insight into the molecular mechanisms of endothelial-pericyte interactions has accelerated during the past 1 to 2 years. Discovery of cytokine regulation confirmed the molecular cell talk between the two types of cells. Intercellular communication between endothelial and mural cells are mediated by many cytokines such as transforming growth factor β , angiopoietins, platelet-derived growth factor, sphingosine-1-phosphate, and Notch ligands and their respective receptors [42]. Bergers and

Song [45] reported that Endothelial-derived PDGF-BB and HB-EGF coordinately regulate pericyte recruitment during vasculogenic tube assembly and stabilization (Figure 2).

Figure 2. PDGF-B/PDGFR- β signaling is necessary for pericyte recruitment during angiogenesis. PDGF-B is synthesized and secreted by the migratory tip cells at the leading edge of angiogenic sprouts. Binding of PDGF-B to HSPG is important for localization of PDGF-B to the vicinity to the developing vessel. Pericytes, which express PDGFR- β , are dependent on of endothelium-derived PDGF-B for proliferation and migration [42].

Pericytes and pathological disorders: Pericyte as a multipotent progenitor cell of pathophysiological importance is gaining increasing attention. Bergers and Song [45] reported that when vessels lose pericytes, they become hemorrhagic and hyperdilated, which leads to conditions such as edema, diabetic retinopathy, and even embryonic lethality. Motegi, et al [46] studied the role of Pericyte-Derived MFG-E8 Regulates Pathologic Angiogenesis. Recent interest in pericytes also stems from their potential involvement in diseases [43-47] such as diabetic microangiopathy [48, 49] tissue fibrosis [50] cancer [51] atherosclerosis [52] and Alzheimer's disease [53, 54].

6. Mesh-induced foreign-body reaction in hernea

The fact that tissue cells respond to biomaterial implantation is illustrated by granuloma formation and cell infiltration surrounding mesh materials over time. Common cellular components of such a reaction are infiltrating macrophages. These cells have the propensity to synthesize a plethora of pro inflammatory cytokines [transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF)) and are regarded as key players directing the extent of fibrosis with influence on the phenotypic behavior of surrounding fibroblasts [55, 56].

Residential fibroblasts independently contribute to the regulation of tissue remodeling and wound healing. They occur as activated myofibroblasts encapsulating the mesh filaments and are constitutionally involved in extracellular matrix (ECM) remodeling by synthesizing type-I and type-III collagen. Furthermore, fibroblasts are the source of enzymes involved in matrix

degradation such as matrix metalloproteinases (MMPs) that may affect the ongoing foreign-body reaction. MMPs are the most abundant proteases in wound healing [57] and MMP-2 (72-kDa collagenase, gelatinase A) enzymatic activities are up-regulated in diseases associated with inflammatory reaction such as arthritis [58], cancer [59], atheroma [60] and tissue ulceration [10]. A pivotal role for MMP-2 in hernia disease was determined by a study that detected elevated levels of MMP-2 enzymatic activity in wound fluids of hernia patients [61].

Beyond their capability to hydrolyze components of the ECM, MMP-2 directly affects cellular phenotypes, proliferation rates and the inflammatory reaction, and several studies indicate that MMP-2 is centrally involved in the inflammatory and fibrotic response [62]. Regarding foreign-body reaction, it is known that macrophages are activated by polymeric nanoparticles and secrete MMP-2 in vitro [64]. Blockage of MMP-2 activation with MMP inhibitor Ilomastat dampens the inflammatory cell infiltration, indicating that MMP-2 mediates the cross-talk of cells and ECM components [65]. In vivo, stimulation of MMP-2 expression may result from a complex cross-talk between cells, especially fibroblasts and macrophages in wound healing. These findings hint at a pivotal role of MMP-2 in wound healing and foreign body reaction and suggest the investigation of the molecular mechanisms that govern MMP-2 gene transcription after biomaterial implantation [66].

Transgenic as well as knockout models were established to elucidate the underlying gene regulation required for wound healing [64]. Meshes interfere with MMP-2 gene regulation due to soluble factors, ECM modification or cell cross-talk. In MMP-2/Lac Z transgenic mice the impact of mesh implantation on MMP-2 gene expression can be evaluated and compared to MMP-2 enzymatic activity, protein synthesis and expression/binding of transcription factors [66].

7. Dendritic cell–NK cell cross-talk

The interaction of NK cells with the professional antigen-presenting cells of the immune system, the dendritic cells (DC), in regulating both innate resistance and adaptive immunity. DC is antigen-presenting cells, cornerstones between pathogen entry and lymph nodes that quickly respond to foreign antigens. Located in peripheral organs, skin, and mucosal surfaces, DC sample the environment for self and foreign material [67].

The molecular mechanisms involved in NK cell triggering by human DC start to be unraveled. Mature DC or immature DC in the presence of maturation stimuli, such as LPS or *Mycobacterium tuberculosis* or IFN, are able to activate NK cells [68, 69]. The crucial role of IL-12 in IFN-secretion by + human NK cells stimulated by monocyte- or CD34 –derived DC and LPS or by peripheral blood m DC in response to TLR3 or TLR8 legends has been formally demonstrated. Other cytokines, such as IL-18, and/or cellular contacts are also involved [70, 72]. However, NK cell activation by DC also requires direct cell-to-cell contacts and depends on the adhesion molecule LFA-1 [73].

The formation of DC/NK cell conjugates was found to depend on cytoskeleton remodeling and lipid raft mobilization in DC. BM-DC derived from mice with loss of function of the Wiskott Aldrich syndrome protein, a major cytoskeletal regulator expressed in hematopoietic

cells; fail to promote NK cell lytic activity and IFN-secretion [71]. Moreover, disruption of the DC cytoskeleton with pharmacological agents abolished the DC-mediated NK cell activation. Therefore, the cross-talk between LPS-activated DC and NK cells is dictated by functional synapses [71].

8. Cellular interaction in normal and fibrosed heart muscle fibers

Cells in the heart interact through both paracrine and autocrine pathways and by direct contact with the formation of gap and adherens junctions and desmosomes. In adherens junctions cadherins on one cell bind to cadherins on another cell in contact and link intracellularly to the actin cytoskeleton via catenins. Desmosomes link to intermediate filaments. Adherens junctions and desmosomes mechanically connect cardiomyocytes and so distribute contractile force within the myocardium. Gap junctions provide intercellular channels for ionic communication that allows the rapid and coordinated spread of excitation throughout the heart [74].

The conversion of fibroblasts to myofibroblasts is central to the development of cardiac fibrosis in response to hypertension [75] in ventricular hypertrophy, hypertension, or infarction; the number of fibroblasts in the heart has been shown to increase [75]. A scar tissue formed after myocardial infarction also is stiffened by both reparative fibrosis and actively contracting cardiac fibroblasts. These myofibroblasts influence myocardial function by increased collagen secretion and contractility causing a stiffening of the heart muscle that can lead to diastolic dysfunction and heart failure [76] and also by possibly interfering with the electrical connectivity of the cardiomyocytes [75]. In this example Genin et al described how tissue constructs serve as model systems in which to study how fibroblasts and cardiomyocytes interact to control contractile force and tissue stiffness. They dissect here the electrical and mechanical cell-cell phenomena that might underlie the above observations. [74]

From the mechanical perspective, a possible explanation is that the eventual domination of the construct by the proliferative myofibroblasts stiffens the tissue constructs in a way that retains the ability to produce a steady baseline force, perhaps exerted mainly by myofibroblasts, while losing the ability to generate myocyte-dependent twitch force. The stiffening of fibrotic myocardium can result from secretion of excessive ECM from the myofibroblasts [77], and likely from increased ECM remodeling and increased myofibroblast contractility as well. The stiffening of the extracellular environment by myofibroblasts and associated rise in baseline force may overwhelm the actomyosin contractile mechanism in the cardiac myofibroblasts, constraining it to a low number of cross-bridge connections by limiting the motion of the contractile apparatus.

In addition to these mechanical effects, myofibroblasts can impair both heart and EHT contractile function by distorting excitatory conduction. Under normal conditions the numerous fibroblasts in the heart maintain the ECM that provides the underlying structure for a continuous network of cardiomyocytes in electrical contact via gap junctions. The spread of electrical excitation in this network is organized to stimulate an orderly contraction first of the atria and then the ventricles to promote optimal pumping efficiency of the heart. Evidently, the

presence of the fibroblasts in normal heart muscle does not perturb this orderly impulse conduction. Myofibroblasts can distort the propagation of the excitatory wave both by disrupting the normal interactions (gap junction formation) among the cardiomyocytes and by forming gap junctions and therefore electrical contact with the cardiomyocytes [74].

Myofibroblasts can be coupled electrotonically to cardiomyocytes in vitro via gap junctions mediated by the connexins Cx43 and Cx45 [78, 79]. In these experiments strands of cardiomyocytes were coated with cardiac fibroblasts that had converted to the myofibroblast phenotype [74].

This coupling suggests that myofibroblasts might not only provide a barrier to the electrical interaction of cardiomyocytes but might also provide a conductive link between them. This was demonstrated in vitro by connecting two strands of neonatal rat ventricular cardiomyocytes by a band of cardiac myofibroblasts [80].

These experiments demonstrate that myofibroblasts both distributed throughout the heart muscle and in border zones of healing infarcts can play a complex role in impulse propagation, imposing steric blockage, providing alternative but slower conduction pathways and predisposing the tissue to arrhythmia [77]. Finally, a model system similar to that described above has demonstrated that contact with myofibroblasts can cause spontaneous activation of cardiomyocytes that could be analogous to ectopic activity in the heart [78].

9. Cell- cell interaction in lung parenchyma cells

Cellular interactions in lung parenchyma were reviewed by Fehrenbach, 2001 [81]. The main functional units of lung parenchyma are the alveoli; an air filled sacs. Alveoli are lined by two types of cells; alveolar type I (type I pneumocyte) which are of considerable little thickness allowing gaseous exchange between alveolar air and pulmonary capillaries forming what is known as blood-air barrier Figure (3, 4).

Figure 3. A: showing scanning microscopy of two great alveolar cells (Type II pneumocytes) B: alveolar cells (Type II pneumocytes) stained by immunofluorescence for surfactant protein D (green). Quoted from Fehrenbach [81].

The second type of cells is alveolar type II or great Type II pneumocyte which is usually cuboidal in shape and rich in organelles involved in secretion of phospholipid material known as surfactant [81].

10. TypeII-type I- alveolar cell interaction

Cell- cell interaction is well represented in lung parenchyma between type II alveolar cells and other resident cells of the lung . Direct laterl cell-cell contact with type I alveolar cell is maintained by cell junction complex that induce gap junction [82]. This contact allow mechanical stimulation of type I cell to modulate exocytosis rate of surfactant secteted by type II via transimmision of calcium ion oscillation throuhgh gap junction. On the other hand, direct inhubitory interaction between the two cells have been postulated by Mason and McCormack [83] to supress Type II proliferation. This explain proliferative activity of the later in case of injury of type I pneumocytes. Type II pneumocyte also was proposed by Kapanci et al. [84] as stem cell of the adult that differentiate to Type I pneumocyte and subsequent repair and re-establishing of air – blood barrier [85, 86].

11. TypeII-typeII interaction

Khalil et al. [87] reported that inhbiton of alveolar type II cells can be mediated via paracrine action via Type II cell-derived transforming growth factor (TGF) as in case of bleomycin-induced experimental lung fibrosis.

Removal of cells dying by apoptosis is essential to normal development, maintenance of tissue homeostasis, and resolution of inflammation. Surfactant protein A (SP-A) and surfactant protein D (SP-D) are high abundance pulmonary collectins implicated in apoptotic cell clearance in vitro. Other collectins, such as mannose-binding lectin and the collectin-like C1q, have been shown to bind to apoptotic cells and drive ingestion through interaction with calreticulin and CD91 on the phagocyte in vitro. However, only C1q has been shown to enhance apoptotic cell uptake in vivo. Similar to C1q and mannose-binding lectin, SP-A and SP-D bound to apoptotic cells in a localized, patchy pattern and drove apoptotic cell ingestion by phagocytes through a mechanism dependent on calreticulin and CD91. These results suggest that the entire collectin family of innate immune proteins (including C1q) works through a common receptor complex to enhance removal of apoptotic cells, and that collectins are integral, organ-specific components of the clearance machinery [88].

12. Alveolar-endothelial cell interaction

Embryonic studies showe that pulmonary endothelial cells exhibit inductive activity on foetal lung alveolar epithelium [89]. This effect was well studied in tissue culture. A paracrine mechanism of action was suggested to be exerted on alveolar cells via endothelin cytokine produced by capillary endothelium. on the other hand, cellular interaction is well represented by the fact that alveolar type II cells may act as transducers of an inflammatory signal from the alveolus to the capillary endothelium

13. Cell- cell interaction between type II alveolar cells and mobile interstitial pulmonary cells

Lung stroma or interalveolar connective tissue is rich in mobile cells needed for pulmonary defense mechanism, those cells include alveolar macrophage derive from circulating monocytes.

14. Type II alveolar- alveolar macrophage - interaction

This type of interaction was represented by reciprocal effect on proliferation of both cells via cytokines production such as hepatocyte growth factor [90] and heparin-binding epidermal growth factor-like protein secreted by macrophage and RANTES and MCP-1 produced by alveolar type II cells [91]. Furthermore, Stamme et al. [92] reported that SP-A released from AE2 cells may modulate macrophage functions such as, oxygen radical release [93], and nitric oxide production [92].

15. Type II alveolar- leucocyte interaction

Cytokines produced by type II alveolar cells were reported to influence differentiation of leucocytes (neutrophils-basophiles and eosinophils) and have a role in lung parenchyma inflammatory reactions. On the other hand, alveolar type II cells can exert inhibitory effect on lymphocytes. Direct interaction of pneumocytes with migrating monocytes was reported to be mediated by β_2 -integrins CD11b/CD18 and β_1 -integrins as well as by CD47 [94]. The concept of considering type II alveolar cells as the “defender of the alveolus” by Fehrenbach, 2001 implies that severe damage or loss of AE2 cells results in a considerable vulnerability of the alveolus such as lung fibrosis [95]. In spite of all knowledge reported by Fehrenbach [82], he added that more studies of mystery of cell-cell interactions of AE2 cells still remains to be expanded.

16. Type II - Fibroblasts interaction

Findings reported by Fehrenbach [82] and Shannon & Deterding 1997 [96] showed that reciprocal cell-cell relationship between type II alveolar cells and fibroblast control the modelling of alveoles during lung morphogenesis as well as during remodelling associated with alveolar repair following lung injury [97, 98]. Both direct and indirect cell-cell interactions have been reported.

Alveolar E2 cells have been reported to secrete a factor that either inhibits or stimulate fibroblast proliferation [99, 100]. In contrast, however, an increase in fibroblast proliferation was seen if both cell populations grown in coculture were able to establish direct cell-cell contacts [100]. Transmission electron microscopy has demonstrated structural interaction between fibroblast processes and type II alveolar cell membranes [99]. Immunoelectron microscopy indicated that CD44v6 is localised at the tips of these foot processes [97]. The CD44 molecules constitute a family of integral membrane glycoproteins

that act as receptors of hyaluronan and osteopontin, for example, and are well established as being involved in epithelial cell migration and differentiation [101]

17. Cell- cell interaction in mammalian testicular tissue

The mammalian testis represented a mixed gland where the exocrine; the seminiferous tubules is responsible for male gamete formation in the process named spermatogenesis. While interstitial (Leydig) cells form the endocrine part that is involved in testosterone production.

Seminiferous tubule presents a highly complex cellular interacting system. Well documented interactions and communications take place between Sertoli and germ cells at different stages of their development [102]. At morphological level, Sertoli cell in testis of many species is associated with ~30–50 germ cells at each stage of the spermatogenic cycle in the epithelium. In his interesting article concerning Cell Junction Dynamics in the Testis Yan Cheng and Mruk [103] mentioned that germ cells largely rely on Sertoli cells for structural and nutritional support [104]. Blood-testis barrier (BTB) formed by tight Junction between the lateral of Sertoli cells [104-108]. Serves for isolation of developing haploid germ cells from body immune response. In addition, cell-cell communications via paracrine factors and signaling molecules were also observed. Sertoli cells in this way can provide developing germ cells with the needed nutrients and biological factors [109-110]. Germ cell-Sertoli cell interactions were studied early by Zabludoff et al [111] who found that regulation of CP-2 (a novel Sertoli cell product) synthesis and secretion by the Sertoli cell is dependent on paracrine signals or direct cell contact with the germ cells.

The findings of Sharpe et al [113] showed that the functions of all of the cell types in the testis are interwoven in a highly organized manner. the authors emphasize that in normal adult rat testis there is a complex interaction between the Leydig cells, the Sertoli (and/or peritubular) cells, the germ cells, and the vasculature, and that testosterone, but not other Leydig cell products, plays a central role in many of these interactions, they added that The Leydig cells drive spermatogenesis via the secretion of testosterone which acts on the Sertoli and/or peritubular cells to create an environment which enables normal progression of germ cells through stage VII of the spermatogenic cycle. In addition, testosterone is involved in the control of the vasculature, and hence the formation of testicular interstitial fluid, presumably again via effects on the Sertoli and/or peritubular cells.

18. Cellular interaction in mammalian skin

Skin is the largest body organ which serves a number of important functions for the welfare of the organism. It has unique structure being derived from two different embryonic sources, namely the ectoderm which give rise the outer epithelial component, the epidermis and epidermal derivatives and the mesoderm which are the source of dermal connective tissue elements [114].

To be an effective body barrier cellular interaction either via structural or cytokine contact between both epidermal and dermal components of skin. Epithelial-mesenchymal interactions control epidermal growth and differentiation. It was found that reciprocal stimulatory effects between keratinocytes and dermal fibroblasts and micro vascular endothelial cells via induction of paracrine growth factor gene expression. The superficial epidermal layer of skin consists of a variety of cells, namely, keratinocytes, the dominant cell type, melanocytes, the coloring cells of skin, Langerhan cells responsible for epidermal defense and Merkel sensory cell [115].

Cell talk is will represented in the process of skin pigmentation (Melanogenesis). Melanin is synthesized and packaged in organelles containing melanogenic enzymes (tyrosinase gene family of proteins), the melanosomes, which are trans located down to the tips of the melanocyte dendrites and then transferred to the neighboring keratinocytes, where they form melanin cap over the nuclei to protect DNA from UV damage [116-117]. Many researches confirmed the presence of cellular interaction between melanocyte and keratinocytes for regulation of skin pigmentation [118-120] which in case of failure result in pathological pigmentation.

Solar Lentigo; macular brown pigmentation appearing after chronic sun exposure is considered as a component of photoaging. Lesional keratinocytes express enhanced levels of endothelin-1 (ET-1) [121] and (stem cell Factor) SCF [122] that stimulate melanocyte proliferation and melanin formation.

Ephelides (Freckles) which are small, discrete brown macules usually <0.5 cm in diameter appear on exposed areas among children and young adults, especially in fair-haired and fair-skinned individuals [123]. Histologically, the melanocytes are normal or reduced in number when compared with adjacent normal skin, but melanin production is increased owing to UV stimulation. Large numbers of mature melanosomes are evident in dendritic melanocytes [124].

Post-inflammatory Hyperpigmentation following inflammation occurring mainly in Fitzpatrick skin types IV-VI [123]. Post-inflammatory hyperpigmentation (PIH) represents a pathophysiological response to cutaneous inflammation, such as acne, atopic dermatitis, discoid lupus erythematosus, erythema dyschromicum perstans, fixed drug eruption, generalized drug eruption, idiopathic eruptive macular pigmentation, impetigo, insect bites, irritant and allergic contact and photocontact dermatitis, lichen planus, lichen simplex chronicus, morphea, pityriasis rosea, polymorphous light eruption, psoriasis, burn, abrasive and postsurgical trauma, and viral exanthem [125]. Melanocytes can either be stimulated by the inflammatory process to become hyper-functional, thus secreting more melanin, or the number of melanocytes can increase. Epidermal hyperpigmentation (such as that associated with acne) occurs when increased melanin is transferred to keratinocytes, whereas dermal pigmentation (e.g., associated with lichen planus and cutaneous lupus erythematosus) occurs when the basement membrane is disrupted causing melanin to fall into the dermis and resides within melanophages [125].

19. Keratinocyte-Langerhans cell interaction

Skin is an immunological organ consisting of epidermal cells, i.e. keratinocytes and Langerhans cells (LCs, antigen-presenting dendritic cells), and both innate and acquired immune systems operate upon exposure of the skin to various external microbes or their elements [126].

Langerhans cells are dendritic cells (antigen-presenting immune cells) of the skin and mucosa, and contain large granules called Birbeck granules. They are present in all layers of the epidermis, but are most prominent in the stratum spinosum [127]. These Birbeck granules, are rod-like membrane-bound structures with regular cross-striations, one end of which frequently distends in a vesicle so that they resemble a tennis racket or Ping-Pong paddles (15 to 50nm in length and 4 nm thick). These granules form as a result of clathrin-assisted endocytosis; however, their function is not known [127, 128].

Langerhans cells derive from the cellular differentiation of monocytes with the marker "Gr-1" (also known as "Ly-6G/Ly-6C") [129]. In skin infections, the local Langerhans cells take up and process microbial antigens to become fully functional antigen-presenting cells. Presenting the processed antigens to T cells resulting in T-cell differentiation and activation has an important role in innate cutaneous immunity [130]. Toll-like receptors (TLR) are involved to enhance the ability of LCs to present a specific antigen to T cells [127]. Toll-like receptors (TLRs) are a class of conserved receptors that recognize pathogen-associated molecular patterns (PAMPs) present in microbes [131]. Hari et al. also reported that these receptors are expressed on several skin cells including keratinocytes, melanocytes, and Langerhans cells [131].

20. Cell-cell interaction in dermal resident cells

Dermis is the deep connective tissue component of skin; it is the habitat of many cells either fixed (permanent) or transient visitors. Fibroblasts represent the dominant population of cells with only few hematopoietic cells residing in these tissues [132]. These cells are responsible for collagen production and serve to maintain the extracellular matrix and stromal connective tissues. They do this by secreting compounds that serve as precursors to components of the extracellular matrix, which go on to form collagens, glycosaminoglycan's, glycoproteins, and reticular and elastic fibers. Fibroblasts has well known role in wound healing processes [133] as well as abnormal scar formation [134]. Adipocytes aggregate under the dermal tissue to offer a secondary protective barrier to body organs.

Dermal cell interaction was described in normal as well as in pathological conditions of human skin. A complex pattern of cell talk or cellular interaction was observed by Ali et al. [134] in case of keloid scars. Fibroblast-lymphocytes, mast cells and macrophages contact were described by authors in such lesions (Figure 4, 5). Walsh et al. [135] reported the role of human mast cells as "gatekeepers" of the dermal microvasculature and indicate that mast cell products other than vasoactive amines influence endothelium in a proinflammatory fashion. Mast cells of considerable number, size and degranulation were found by Ali et al. [134] to dominate in some lesions of keloid scar. This suggested the interaction between

those two cells and their implication in scar formation. A paracrine loop between adipocytes and macrophages via free fatty acid and free fatty acids and tumor necrosis factor alpha signaling was reported by Suganami et al [136] and Andrade et al. to aggravate inflammatory changes [137].

Figure 4. Cell interaction between different cell population in keloid dermal connective tissue, Quoted from Ali et al. [134].

The extracellular matrix is important because its composition determines the physical properties and integrity of dermal connective tissue [128]. Fibroblast growth factor (FGF) signaling is involved in a wide range of important organically activities with differential effects in several cell types. Ali et al. [134] found an interesting association of fibroblasts with lymphocytes, mast cells and macrophages known to be increased in dermal tissue in case of inflammatory processes characterized skin injury. A sort of cell interaction seemed to occur between fibroblasts and these immune cells was suggested. This interaction was termed cell talk by Lim et al [138].

Mast cells were the third type of immune cells that were interestingly found in large numbers of keloid scars examined in this study. This explained the finding that most patients with abnormal scars complained of itching as a symptom and erythema as a sign [139-140]. Both resolved by corticosteroid treatment. In this study, mast cells were found in

close contact with fibroblasts. Mast cell activation is a characteristic feature of chronic inflammation, a condition that may lead to fibrosis as a result of increased collagen synthesis by a fibroblast [140-144].

Fibroblasts were also found to produce a mast cell growth factor that supposedly regulates mast cell survival, differentiation, and granule synthesis, whereas, mast cells were shown to affect the biochemical properties of fibroblasts, which can lead to fibrosis. Fibroblasts can modulate the functions of both mast cells and eosinophils, which also increase the amount of melanocytes and melanin pigment [141-143].

Obesity is associated with decreased dermal elasticity. This denotes the presence of an adipocyte–fibroblast interaction. Azure and Amano [145] found that enlarged adipocytes have negative regulation of dermal fibroblasts through release of free fatty acids.

Figure 5. Mast cell-lymphocyte interaction by scanning microscopy, Quoted from Ali et al. [134].

Eosinophil infiltration into the inner dermal compartment is a predominant pathological feature of atopic dermatitis [146]. The interaction between eosinophils and fibroblasts under IL-31 and IL-33 stimulation differentially activated extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38 mitogen-activated protein kinase, nuclear factor- κ B and phosphatidylinositol 3-kinase–Akt pathways.

Eosinophil infiltration into the inner dermal fibroblast layer causing inflammation in atopic dermatitis has been well established]. Investigation of the interaction between eosinophils and fibroblasts may therefore help to elucidate the mechanism of initiating local inflammatory response in atopic dermatitis [147].

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