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Mesothelial-mesenchymal transitions in embryogenesis

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ABSTRACT

Most animals develop coelomic cavities lined by an epithelial cell layer called the mesothelium. Embryonic mesothelial cells have the ability to transform into mesenchymal cells which populate many developing organs contributing to their connective and vascular tissues, and also to organ-specific cell types. Furthermore, embryonic mesothelium and mesothelial-derived cells produce essential signals for visceral morphogenesis. We review the most relevant literature about the mechanisms regulating the embryonic mesothelial-mesenchymal transition, the developmental fate of the mesothelial-derived cells and other functions of the embryonic mesothelium, such as its contribution to the establishment of left-right visceral asymmetries or its role in limb morphogenesis.

1. Introduction

Development of the epithelium was a major milestone in metazoan evolution. Epithelial organization of cells provided the animals with a physical and functional barrier between organism and the external environment, as well as closed cavities where fluid composition can be controlled. This innovation is so important from an evolutionary point of view that the term Epitheliozoa has been used for the clade joining the Homoscleromorphan sponges, Placozoans and Eumetazoans; i.e. the vast majority of the animals [1]. The importance of the epithelial organization is reflected in ontogeny. Epithelial E-cadherin is already expressed in the 8-cell stage of murine embryos and it is required for trophoectoderm formation and blastomere adhesion [2]. Loss of function of E-cadherin arrests the development at a very early stage [3].

Epithelial cells show apical-basal polarity (they are attached to the neighboring epithelial cells through tight junctions and lie on a basement membrane). On the other hand, mesenchymal cells are motile and fibroblast-like, showing front-rear polarity, and establishing loose interactions with other cells without tight intracellular adhesions. Mesenchyme is defined in the Merriam-Webster dictionary as "loosely organized undifferentiated mostly mesodermal cells that give rise to such structures as connective tissues, blood, lymphatics, bone, and cartilage". Thus, "mesenchyme" should not be used as synonym of "mesoderm", since mesenchymal cells from ectodermal origin (such as the neural crest cells) also fit with this definition. In addition to this, mesoderm frequently adopts an epithelial phenotype (eg. somites, lateral mesoderm).

Epithelial and mesenchymal phenotypes are exchangeable during development. Cells from an epithelium can lose lateral adhesions, degrade basal lamina and migrate through the extracellular matrix in a process called epithelial-mesenchymal transition (EMT). On the other hand, mesenchymal cells can establish tight adhesions between them, secrete a basal lamina and organize a new epithelial sheet. This reverse process is known as mesenchymal-epithelial transition (MET) [4]. Although both processes are normally restricted to the embryonic period, they can be recapitulated during adulthood (commented in the Section 6 of this review) participating in reparative and pathological processes.

Mechanisms regulating EMT and MET have attracted attention of many research groups in recent years as these developmental processes are similar to those used by cancer cells to disseminate and seed metastases from a primary tumor [5]. Rounds of EMT and MET occur during the embryonic development of bilaterians in what is considered a key mechanism of evolutionary innovation in Metazoans [6].

A mesodermal epithelium, in most animals, coats an internal cavity called the coelom. This cavity facilitates the movement of contractile organs (heart and gut) and constitutes a primitive means by which to distribute nutrients and homogenize the inner medium in animals lacking a well-developed circulatory system. Taxonomic classifications at-

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tributed evolutionary significance to this feature in the past and divided bilaterian metazoans in acoelomates, pseudocoelomates and coelomates. We know now that the coelomic cavity has appeared and disappeared in different lineages, and it is known that several processes lead to coelomogenesis and that the origin of the mesoderm is different in Protostomes and Deuterostomes (although a common set of genes from the developmental toolkit is used in both cases) [7]. However, in all cases, the coelomic cavity is lined by an epithelium of mesodermal origin called the mesothelium. In other words, all the organs in association with or limiting with coelomic cavities, the inner (peritoneal) surface of the body wall and all the regions of mesentery are lined by a mesothelium. The embryonic mesothelium is able to respond to local signals and generate mesenchymal cells through an EMT. This article focusses on the processes of EMT that occur in embryonic mesothelium and with the fate of the mesenchymal cells generated from these processes.

An important preliminary issue is the use of the term "mesothelium" when we refer to the coelomic epithelium of the embryo. Any epithelium of mesodermal origin could be considered a mesothelium *lato sensu* (this includes specialized tissues such as the endothelium). We will use the term "mesothelium" in this review as equivalent to "coelomic epithelium" for the sake of simplicity. However it is important to note that embryonic mesothelium has important differences when compared with the adult one. For example, the embryonic mesothelium is able to respond to local signals generating mesenchymal cells, and it shows co-expression of epithelial and mesenchymal cytoskeletal proteins such as cytokeratins and vimentin [8]. Strictly speaking, we should only use the term mesothelium when the splanchnopleural and somatopleural mesodermal cell layers lining the coelomic cavity (1) express E-cadherin in their lateral adhesions and (2) when they overlie a basement membrane. However, these features appear in a dynamic and reversible manner in embryonic mesothelium [9].

Only certain regions of the splanchnopleural or somatopleural mesoderm become mesothelium through a MET. Thus, the stroma of visceral organs can have two different origins, from the primitive lateral mesoderm that never become a mesothelium, and from the embryonic mesothelium, through an EMT. As we will describe in this review, in many cases, mesenchymal cells from both sources mix performing similar or identical functions, and sharing a similar developmental fate. Thus, mesothelial EMT cannot be considered as a mechanism to generate organ-specific cell types but rather to supplement the stromal component of rapidly developing organs [10].

Mesothelial EMT has acquired greater attention and recognition of its importance in recent years. We currently know that a number of organ-specific cell types derive from an embryonic mesothelium, a cell layer that also produces signals required for proper morphogenesis of organs they invest. Evidence also suggests that the adult mesothelium plays an active role that can be linked to the embryonic relationships between organs and their covering mesothelium. We aim to review information about the molecular mechanisms that regulate the embryonic mesothelial-mesenchymal transition, the developmental fate of the different populations of mesothelial-derived cells, and its contribution to the establishment of left-right visceral asymmetries and a role in limb morphogenesis.

2. EMT/MET: basics of molecular regulation

Stability of the embryonic epithelia and control of the migratory ability of mesenchyme is critical for accurate morphogenesis. Transitions between cell phenotypes must be regulated by a number of molecular agents including exogenous signals, transduction pathways, transcription factors and epigenetic modulators [4,11]. The balance between these regulators determines the epithelial or mesenchymal phenotype of cell as well as its behavior (Fig. 1). A key role is played by the transcription factors that repress E-cadherin expression. As stated above, E-cadherin is an essential molecule for the tight junction formation between epithelial cells and its repression represents the early event in an EMT. When E-cadherin is repressed, β-catenin, also involved in regulation of intercellular adhesions, loses its interaction with the cytoskeleton and it is either degraded or stabilized in response to canonical Wnt signaling, acquiring transcriptional activity [11]. The number of transcription factors (TFs) that can trigger an EMT is surprisingly high and includes members of the zinc-finger family (Snail1,2,3), E-Box binding proteins (Zeb1,2), bHLH (Twist1,2) and Forkhead box (Foxc1,2) [12]. Among them, it is important to note the evolutionarily role played by Snail and Twist factors whose role in E-cadherin expression is highly conserved [4].

Epigenetic regulation of transcription factor activity is also important. For example, the small non-coding RNA miR200 and miR34 target Zeb1 and Snail1, respectively. Thus, a network of crossed interactions between these miRNAs and TFs controls the balance between cell phenotypes [4].

Among the signals that can elicit EMT, members of the TGFβ and FGF families of secreted factors are the most important, signaling through serin/threonine kinase and tyrosin kinase receptors, respectively. Other tyrosin kinase receptor ligands and Notch, Wnt and Hedgehog signaling can also induce EMT [13].

EMT also involves activation of small GTPases involved in regulation of actin dynamics, cell polarity change and cell motility. RhoA promotes actin stress fiber formation, while Rac1 and Cdc42 regulate the development of lamellipodia and filopodia [11]. The role of RhoA is complex since it is required for EMT, but it must be downregulated in the basal region of the epithelial cells for basement membrane breakdown [14,15], and RhoA loss of function promotes EMT [16]. This explains that upregulation of RhoA abrogates EMT in somatopleural mesothelium [17].

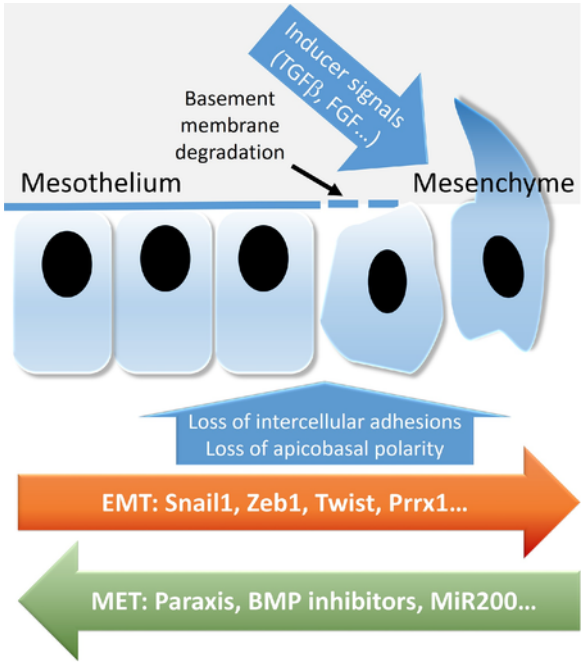

Fig. 1. Outline of the mesothelial-mesenchymal transition. Inducer signals such as TGFβs and FGFs lead to the expression of transcription factors (Snail, Zeb1 or Twist) that repress E-cadherin and other epithelial genes and induce the initiation of a "mesenchymal program" that includes degradation of the extracellular matrix, acquisition of front-rear polarity and motility. Mesenchymal cells can also revert their phenotype and transform into an epithelium. This is regulated by Paraxis in the case of the somite, and probably by inhibitors of BMP and other factors in the lateral mesoderm.

The molecular regulation of the MET is less well characterized and appears to involve repression of the EMT activator factors. This regulation can be clinically significant since a MET event is likely related with the establishment of secondary tumors [18]. Somitogenesis is a developmental MET process that requires Paraxis expression (a bHLH transcription factor) and Snail repression. This process is controlled by Rac1 and CDC42, a protein involved in regulation of the cell cycle [19–22]. However, the factors leading to the formation of epithelial-like sheets in the lateral mesoderm (see next section) are unknown. Since BMP is an activator of Snail and other EMT inducers [23], BMP inhibitors could be candidates for the termination of developmental EMT processes. Significantly, cessation of the gastrulation is probably mediated by the activity of the BMP-antagonist Noggin [24].

The maintenance of epithelial stability is also important. This is a function of the so-called "epithelial keepers"such as miR200 (which targets Zeb1), the factor Ovol1/2 and p53. RhoA and its effector Rock2 are targets of miR31 and miR-124 respectively, and both inhibit EMT in cancer cells [25]. Specific acetylation of histones H2A and H2B also protects the epithelial phenotype [25].

3. EMT and MET are involved in the formation of the mesothelium

As we stated in the introduction, several rounds of EMT and MET can be identified in the mesodermal tissues during development (Fig. 2). It is feasible that this capacity was key in the development of increased organic complexity in bilaterians [6]. The early blastula of vertebrates is composed of epithelial-like sheets of cells. Gastrulation of amniotes can be considered as a typical EMT, regulated by Snail family members [6,7]. Mesenchymal cells migrating to the sides of the primitive streak regain the epithelial-like phenotype in a MET process. This is regulated by Paraxis, in the case of the epithelial somite, and by other as yet unknown factor(s) in the lateral mesoderm [8]. Inhibition of BMP signaling may be involved in the epithelialization of lateral mesoderm, since exogenous BMP4 interferes with this process [29]. In chick embryos, BMP signaling regulates EMT of the lateral plate mesoderm leading to the morphogenesis of the dorsal mesentery, and it activates the EMT factor Snail2 [30]. BMP inhibition also mediates the cessation of gastrulation, as stated above [24].

The lateral mesoderm forms two layers (somatopleura and splanchnopleura) that acquire an epithelial appearance and leave a space between them (i.e. the developing coelom). The splanchnopleura starts to produce mesenchymal cells early through an EMT-like process. It is unknown if all the splanchnic mesenchyme at this stage or only a fraction arises as a result of an EMT, but the coelomic epithelium of chick embryos is the main source of the mesenchyme in the dorsal mesentery and subaortic area [30]. Anyhow, a mesothelial EMT is activated locally along the embryonic development coinciding with the development of different organs, as described in the next section (Fig. 3). Other EMT events occur in the somite, giving rise to limb myoblasts, or in the mesoderm of the cardiac field, originating the endocardium [22].

4. Developmental fate of the mesothelial-derived cells

Tracking the developmental fate of the mesothelial-derived cells involves directcell labeling with vital dyes or reporter-expressing plasmids. Genetic labeling is also feasible using the Cre-Lox technology (Fig. 4). Mice expressing mesothelial-specific drivers encoding the enzyme Cre-recombinase can be crossed with ROSA-based reporter lines allowing for constitutive expression of markers in cells derived from the mesothelium. The use of inducible drivers, activated after tamoxifen administration enables identification of the optimal time window for the mesothelial labeling [31,32]. This methodology could also be used for tracing mesothelial derivatives in adult life, in order to study the role played by these derivatives during repairing or regenerative processes (see Section 6 for one example).

Among mesothelial drivers, constitutive or inducible Wt1-Cre drivers (based on the Wilms' tumor suppressor gene) have been extensively used. Wt1 is dynamically expressed in areas where the mesothelium is transforming into mesenchymal cells [33], at this point it acts as a repressor of E-cadherin and activator of Snail1 [34] (Fig. 4D,F,G). Wt1 is usually downregulated as soon as mesothelial-derived cells acquire the mesenchymal phenotype, although in some cases expression can persist for some time. It is still not known how Wt1 expression is activated in the mesothelium, but regulation of this expression could be critical for both mesothelial EMT and determining the fate of mesothelial-derived cells [35]. Mesothelin-Cre has also been used for the tracing of mesothelial-derived cells in the trunk, as described below [36].

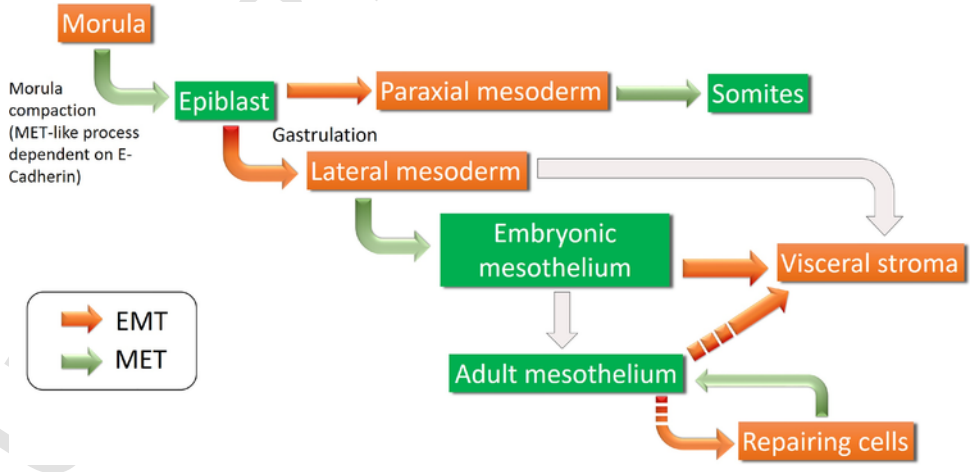

Fig. 2. Rounds of epithelial-mesenchymal transitions (EMT, orange arrows) and mesenchymal-epithelial transitions (MET, green arrows) lead to the formation of the embryonic mesothelium. The visceral stroma derives from both, lateral plate mesoderm and mesothelial EMT. Discontinuous arrows represent postnatal mesothelial EMT events reported in some organs, as described in Section 6.

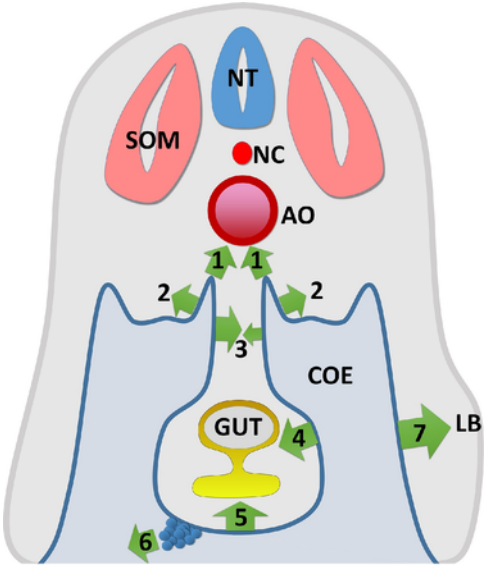

Fig. 3. Main sites of mesothelial-mesenchymal transition. The embryonic mesothelium (blue) undergoes transformation into mesenchyme in different sites, as detailed in the text. 1: Origin of trunk and periaortic mesenchyme, including part of the aortic smooth muscle and thymus stroma. 2: Origin of adrenogonadal and nephric mesenchyme, including adrenal cortex, granulosa, Sertoli and Leydig cells. 3: Asymmetric origin and behavior of mesenteric mesenchyme, contributing to L–R visceral asymmetry. 4: Origin of gut mesenchyme. 5: Origin of mesenchyme of the endodermal viscera (lungs, liver, pancreas). 6: The proepicardium, frequently located at the right side, supplies cells to the heart, where they will constitute the epicardium. The embryonic epicardial cells will give rise to most cardiac mesenchymal cells. 7: Origin of limb bud (LB) mesenchyme, critical for limb development. AO: Dorsal Aorta; COE: coelomic cavity; NC: notochord; NT: neural tube; SOM: somite.

4.1. Cell tracing methodologies have provided a relatively complete picture of the contribution of cells derived from mesothelium to development of tissues and organs. We summarize these contributions in the following section. Epicardium

The epicardium is the mesothelial lining of the heart. The embryonic epicardium gives rise to mesenchymal cells that populate the subepicardial space and invade the myocardium (Fig. 4A,E). This is critical for cardiac development since epicardial-derived cells contribute to most of the coronary smooth muscle and cardiac connective tissue [10]. The contribution of epicardial-derived cells to cardiomyocytes and to the coronary endothelium has been debated. The use of epicardial quail-chick chimaeras ruled out any contribution of epicardial-derived cells to the avian myocardium [37]. In mice, the use of Wt1-Cre and Tbx18-Cre drivers suggested that a lineage of cardiomyocytes derived from epicardial-derived cells, while these cells did not contribute significantly to the coronary endothelium [38,39]. However, the adequacy of Wt1-based lineage tracing systems for epicardial fate mapping is controversial [40,41], and other studies have not found evidence to support the concept of epicardial-derived cardiomyocytes [42]. A separate study using a specific epicardial driver based on a GATA4 enhancer has shown that about 20% of coronary endothelium derives from an epicardial cell lineage [43]. Importantly, the origin of adult cardiac adipose tissue from an epicardial-derived cell lineage has also been demonstrated [44].

Epicardial cells play a signaling role that is essential for the maturation and proliferation of the myocardium. This role is probably mediated by FGFs, IGF2 and erythropoietin, and is dependent of an retinoic acid signaling pathway [45-48].

4.2. Lung

The role of mesothelium during pulmonary development has been extensively studied. Factors secreted by the mesothelium (particularly FGF9) are essential for the morphogenesis of the lungs [49-51]. Less is known regarding the contribution of mesothelial-derived cells to the

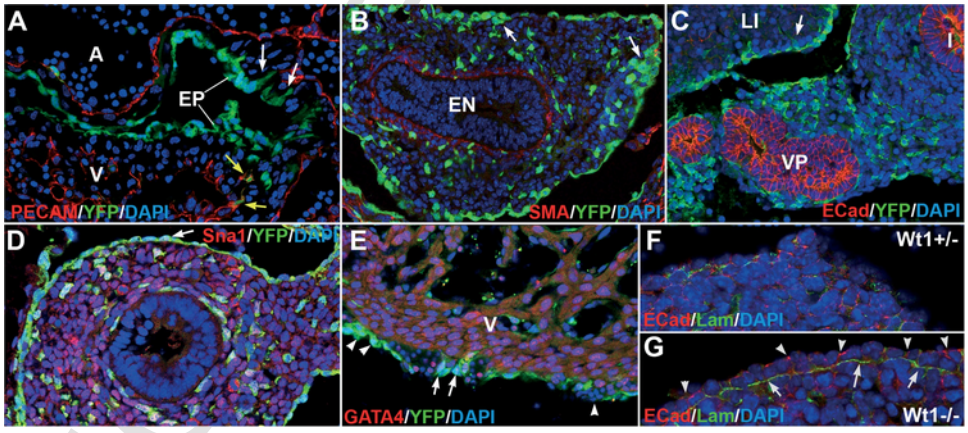

Fig. 4. Images taken from $Wt1^{Cre}$; $R26R^{EYFP}$ embryos are shown in figures A–E. This model is useful to trace the mesenchymal cells that expressed the Wilms' tumor suppressor gene (Wt1) when they still were in the mesothelium [31,32]. **A**: Stage E11.5. The embryonic epicardium (EP) gives rise to mesenchymal cells, especially in the atrioventricular groove (white arrows). Some epicardial-derived cells are expressing the endothelial marker PECAM-1 (yellow arrows). A: atrium; V: ventricle. **B**: Stage 12.5. Lung bud shows many mesothelial derived cells that are apparently migrating from the mesothelium in some hot spots (arrows). In later stages these cells will express smooth muscle α-actin (SMA), a marker of vascular and visceral smooth muscle. EN: endodermal epithelium of the lung. **C**: Stage E12.5. Most mesenchymal cells of the ventral pancreatic bud (VP) are derived from the mesothelium. Note also the signs of migration of mesothelial cell into the liver (LI). I: Intestine.**D**: Stage E12.5. Expression of Snail1 in the developing lung. A few mesothelial cells, probably starting its transformation (arrow) and most mesenchymal cells express Snail1. Note that Snail1 expression occurs in both cells of the Wt1-expressing lineage and cells YFP-negative, which do not derive from the mesothelium. **E**: Stage 12.5. GATA4 expression is heterogeneous in the epicardium. Note homogeneous GATA4 expression in cardiomyocytes of the ventricle (V). GATA4-expressing cells are transforming into mesenchymal cells (arrows). Other epicardial cells are GATA4-negative or even negative for the Wt1 lineage reporter (arrowheads). **F,G**: Liver, Stage 12.5. Expression of Wt1 in the embryonic mesothelium represses the epithelial phenotype promoting mesenchymal transformation. Thus, Wt1-knockout mouse embryos show more epithelial features in the mesothelium. Note the continuous, laminin-positive basement membrane (arrows) and the more homogeneous expression of E-cadherin (arrowheads) in the Wt1-deficient embryo (G).

pulmonary stroma. Que et al. [52], using a Wt1-Cre driver, demonstrated that mesenchymal cells generated by a mesothelial EMT differentiate into vascular smooth muscle cells, interstitial fibroblasts, alveolar myofibroblasts and a few endothelial cells. Cano et al. [53] used a different Wt1-Cre driver and confirmed the pulmonary mesothelial EMT by live imaging, and identified a contribution of mesothelial-derived cells to other tissues such as endothelium, bronchial smooth muscle and cartilage (Fig. 4B). Flow cytometric analyses have shown that by late gestation 3% of all pulmonary endothelium derived from a mesothelial origin. Additionally, Cano et al. [53] also identified a non-endothelial, fibroblast-like population of CD34+ cells (at late gestational stages) also derived from Wt1-expressing mesothelial cells. Similar results have been obtained using inducible Wt1-Cre and mesothelin-Cre drivers [36,54]. However, Greif et al [55]. found no evidence of contribution of mesothelial-derived cells to the smooth muscle of the developing pulmonary artery using a tamoxifen-induced Wt1-Cre driver.

4.3. Gastrointestinal tract

The mesothelium lining the developing gastrointestinal tract also gives rise to mesenchymal cells in turn mix with splanchnopleural mesoderm. Wilm et al. [56], using a Wt1-Cre driver as well as direct cell labeling, showed how a mesothelial-derived population contributed to vascular smooth muscle. Later, Carmona et al. [57] used a different Wt1-Cre driver demonstrating mesothelial contributions to intestinal smooth muscle, a minor fraction of the endothelium and a part of the interstitial cells of Cajal (the intestinal pacemaker cells). As in the case of the lungs, a subpopulation of CD34+, fibroblast-like cells were also partially originated from mesothelial-derived cells.

4.4. Liver

The endodermal liver bud develops in the mesenchyme-rich milieu of the septum transversum. During hepatic development, the mesothelium lining the liver buds generates substantial populations of mesenchymal cells (Fig. 4C). This was first demonstrated in chick embryos through direct labelling [58]. Later, a number of studies showed that the same process occurred in mouse embryos, and that mesothelial derived cells contributed significantly to the sinusoidal endothelium and also to perivascular and hepatic stellate cells [59,60]. As in the case of the heart, the embryonic hepatic mesothelium also plays a signaling role, secreting growth factors such as midkine, pleiotrophin and hepatocyte growth factor under control of Wt1 [61]. This observation explains the liver hypoplasia reported in Wt1-deficient mouse embryos [59].

4.5. Pancreas

Like the liver, pancreas development involves molecular interactions between endodermal epithelium and splanchnopleural mesoderm. The role played by the mesothelium in pancreatic development was hitherto unknown. Our recent results [62] show that this mesothelium also generates a large population of mesenchymal cells that contribute to the vascular smooth muscle, endothelium (10% of all the endothelial cells by midgestation, as quantified by analytical flow cytometry) and, importantly, a major fraction of the pancreatic stellate cells, including the islet stellate cells (Fig. 4C). These cells are similar in their phenotype and function to the hepatic stellate cells and they play important roles in physiological and pathological conditions [63,64]. The mesothelial contribution is comparatively higher than the reported in other viscera, accounting for about a half of the stromal component of the developing pancreas. The contribution of coelomic cells to the pancreatic stroma has been confirmed by a recent study [65].

4.6. Spleen

The spleen develops from the splanchnic mesodermal plate, which is a thickening of the coelomic epithelium. Thus, the embryonic mesothelium appears critical in the formation of splenic stroma which is later colonized by hematopoietic cells [66]. In fact, loss of function of the Wt1 leads to complete agenesia of spleen [67]. However, there is no evidence of EMT of the splenic mesothelium giving rise to mesenchymal cells in later stages of development.

4.7. Gonads and adrenals

Involvement of the mesothelium in the development of the genital ridges and the subsequent gonads is long established. The origin of Sertoli cells from the coelomic epithelium of the genital ridges was demonstrated by Karl and Capel in 1998 [68]. More recently, it has become evident that most genes related with gonadal development are first expressed in the mesothelium and then in the specialized stromal cells of the male and female gonad. This occurs for steroidogenic factor-1 (Sf1), Osr1 or Wt1 [69]. In this way, Sertoli and Leydig cells of the testicle and granulosa cells of the ovary are derived from the embryonic mesothelium of the genital ridges [69,70]. This process is dependent of the paired-box gene Emx2 [71]. It is interesting to remark that the corticoadrenal primordium that develops closely associated to the genital ridges also receives a large population of mesothelial-derived cells [72]. Of note, loss of function of Wt1 causes a failure in the development of both adrenals and gonads [73].

4.8. Genitourinary system

Mesenchymal cells derived from the mesothelium covering the nephric ridges are abundant in the developing kidneys, but it is uncertain what the contribution of mesothelial-derived cells to the meso and metanephric mesenchyme is. Some of these cells regain the epithelial phenotype giving rise to the Mullerian duct and other mesenchymal cells differentiate into uterine smooth muscle [74]. However, the Wolffian ducts form from the intermediate mesoderm without contribution of mesothelial-derived cells [75]. In this case, there is a cross-talk between these tissues, since it has been shown, in chick embryos, that the epithelial phenotype of the nephric ridges is maintained by signals from the Wolffian duct [76].

4.9. Body wall and other tissues

The morphogenesis of the dorsal mesentery and its precise localization at the midline of the gut depends on a symmetrical EMT of the lateral plate mesoderm. This is mediated by BMP signaling [30]. As described below (Section 5), asymmetric events involving the dorsal mesentery are involved in the development of visceral left-right asymmetry. The later is critical for correct position of the abdominal organs. It is interesting to remark that expression of BMP2 in the dorsal mesentery of the chick embryo has been related with the differential elongation rates between gut and mesentery, determining the number and tightness of loops in the chick small intestine [77].

Using an inducible mesothelin-Cre driver, Rinkevich et al., [36] showed that many fibroblasts and smooth muscle cells of the trunk, including the aortic smooth muscle, were derived from mesothelial cells. Surprisingly, the stromal component of the thymus also showed a contribution from mesothelial-derived cells. A contribution of mesothelial cells to the aortic wall had been described in chick embryos using direct cell labelling [8].

The origin of mesenchymal cells from trunk mesothelium seems to be critical for formation of coelomic compartments. Pleuropericardial

membranes fail to develop in Wt1-null mice [78]. We have shown that conditional deletion of Wt1 in the lateral mesoderm reduces the amount of mesothelial-derived mesenchyme and impairs the formation of the pleuroperitoneal folds, leading to diaphragmatic hernia formation [72]. Mesothelial-derived cells also contribute to the stromal vascular fraction and the progenitors of the white adipose tissue (both in embryos and adult mice) [79]. This relationship between mesothelial-derived cells and adiposity is also observed in the cardiac fat tissue, as commented above [44], and it appears to correlate with the numerous properties of visceral and subcutaneous adipose tissue [80].

Finally, mesothelial-derived cells have also been linked with the origin of the limbs [17]. Localized EMT of the somatopleural mesoderm supplies proliferating mesenchymal cells that populate developing limb buds. This process is dependent on FGF10 and Tbx5; forced FGF10 expression in the chick somatopleura can induce ectopic limb buds, while Tbx5-null and FGF10 null mouse embryos show a reduction of somatopleural EMT and a failure in the initiation of the limb bud formation [17].

5. Embryonic mesothelium and left-right asymmetry

Recently it has emerged that embryonic mesothelium plays a previously unsuspected role in establishment of visceral left-right asymmetry. Kurpios et al. [81] described how a leftward bent of the gut tube initiates counterclockwise coiling of the intestine. This is caused by an asymmetry in the architecture of the dorsal mesentery in which mesenchymal cells are more condensed on the left side. In addition, left-sided mesothelium is columnar while that on the right has a cuboidal morphology. Morphological asymmetry is associated with asymmetric expression of transcription factors, Pitx2 and Isl1 on the left side and Tbx18 on the right [82]. Later, it was demonstrated that the cytoskeletal protein Shroom3 was required for morphological asymmetry of mesothelial cells. Furthermore, N-cadherin, which is expressed only at the left side of the mesentery, was necessary for asymmetrical mesenchymal condensation. Shroom3 and N-cadherin were downstream of Pitx2 to regulate morphological changes leading to left-right asymmetry of the gut [83]. More recently, it was shown that Pitx2 mediates non canonical Wnt signaling to activate Daam2, a formin-related protein that binds α-catenin and N-cadherin to promote adhesion of mesenchymal cells at the left side of the mesentery. Wnt5a is antagonized at the right side of the mesentery by secreted frizzled-related protein, a factor highly expressed by the mesothelium of that side [84].

EMT inducers such as Prrx1 and Snail1 are also linked to asymmetric generation and migration of mesenchymal cells from the lateral plate mesoderm as well as with morphogenesis of the cardiac inflow tract and cardiac L–R asymmetry [85]. This cannot be considered as a "classical" mesothelial EMT as asymmetric generation of mesenchyme from mesothelium may be related to a higher incidence of congenital diaphragmatic hernia at the left side [72]. Thus, embryonic mesothelium is involved in the establishment of visceral L–R asymmetry through modulation of its architecture, production of molecular signals and asymmetric generation of EMT-derived mesenchyme.

6. EMT in adult mesothelium, clinical significance

The adult mesothelium has long been considered a passive epithelium, whose main function was to reduce friction and avoid adhesions between the viscera. However, new functions for the mesothelium have recently been identified. Adult mesothelial cells sense and react to local environmental signals, they regulate the transport of fluids and cells and have active roles in inflammatory and immune responses [86]. Mechanisms of mesothelial healing after peritoneal damage arise due to the ability of mesothelial cells to detach and adhere selectively to the damaged areas [87,88]. This regenerative capacity has been confirmed by lineage tracing of WT1 expressing mesothelial cells [89].

Adult mesothelial cells retain the embryonic capacity to transform into mesenchymal fibroblast-like cells in some physiopathological conditions (i.e. recurrent peritoneal dialysis). The derivate cells secrete extracellular matrix and contribute to peritoneal fibrosis. This transformation is a true EMT. It is mediated by Snail1 and involves repression of E-cadherin [90]. The knowledge of the molecular mechanisms that regulate this process will be key to reduce the unwanted effects of peritoneal dialysis. Furthermore, the potential role of the epicardium in cardiac repair could also benefit from the knowledge of signaling mechanisms in the embryonic heart [91].

The ability of adult mesothelial cells to recapitulate the embryonic process of EMT raises the question of whether the cells generated might be pluripotential progenitors (reviewed in [10]). It is established that malignant mesothelioma can display osseous and cartilaginous features, and cultured mesothelial cells can differentiate into osteoblast-like or adipocyte-like cells [92]. As we described above, mesothelial-derived cells contribute physiologically to the stromal vascular fraction of the visceral adipose tissue, which is relatively rich in mesenchymal progenitor cells [79]. Cartilaginous differentiation in human peritoneal tissue [94], mesenteric heterotopic ossification (serous metaplasia) and pericardial calcification [94-96] may result from a physiological osteogenic and chondrogenic potential of adult mesothelial cells. Thus, adult mesothelial-derived cells have a differentiation potential that is similar to that observed in mesenchymal progenitor cells. This potential might support the view of the adult mesothelium as a remnant of the embryonic mesoderm.

In vitro, peritoneal explants and adult epicardial cells undergo EMT and develop a smooth muscle phenotype [97,98], in the same way as peritoneal explants can do [99,100]. Surprisingly, adult epicardial cells decrease in number at the surface of the heart in pathological conditions such as myocardial infarct, when they invade the cardiac wall in an EMT-like process [101]. When adult epicardial cells are induced in culture with TGFβ, they acquire mesenchymal features and expressed the stem cell receptor c-Kit. Whether this observation has relevance to physiological mechanisms of cardiac repair, is not known.

7. Concluding remarks

Mesothelial-mesenchymal transitions constitute a set of multiple developmental processes whose regulation at the cellular and molecular levels are still poorly characterized. However, these transitions are critical events as they generate an important population of mesenchymal cells that contribute to the stromal compartment of many viscera and also to organ-specific cell populations. The mesentery itself has been considered as an organ on the basis of having distinctive anatomical and functional features [102], and alterations in the mesentery have been linked with pathologies such as Crohn's disease [103]. Embryonic mesothelial-mesenchymal transition contributes to the cellular organization of the mesentery and it could also be important in adults. Since the anatomical organization of the mesentery in mice is very similar to that of humans [104], transgenic murine models will provide useful insight into human mesenteropathies, either primary or secondary.

Despite the important functions of mesothelial-derived cells, many issues require further attention. It is still unknown how differentiation of mesothelial-derived cells towards their developmental fates is orchestrated in each organ. We do not know if mesothelial-derived cells are multipotential progenitors or if they become committed mesothelium (even if the embryonic mesothelium itself is heterogeneous, see Fig. 4E). Related with this, we ignore how the decision between becoming mesenchymal or remaining epithelial is taken by the mesothelial cell. Another important issue is whether adult mesothelial cells regain embryonic properties to give rise in physiological or pathological

conditions to mesenchymal cells, perhaps with progenitor ability. How can this transformation be controlled? Answers to these questions might be of translational relevance with potential implications for regenerative medicine.

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