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EpCAM in morphogenesis

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1. ABSTRACT

Embryonic development is one of the most complex biological phenomena that involves the appropriate expression and synchronized interactions of a plethora of proteins, including cell adhesion molecules (CAMs). Many members of the diverse family of CAMs have been shown to be critically involved in the correct execution of embryonic development. The Epithelial Cell Adhesion Molecule (EpCAM) is an atypical cell adhesion molecule originally identified as a marker for carcinoma. However, recent insights have revealed that EpCAM participates in not only cell adhesion, but also in proliferation, migration and differentiation of cells. All of these processes are known to be fundamental for morphogenesis. Here, we review the current literature that establishes EpCAM as a protein involved in morphogenesis, starting from the earliest stages of embryogenesis and ending in organogenesis. In addition, we provide directions for further elucidation of the role of EpCAM in embryogenesis.

2. INTRODUCTION

EpCAM is an epithelial cell adhesion molecule, which based on its capability to mediate cell-cell adhesions, has been classified to the broad family of cell adhesion molecules (CAMs). However, EpCAM is an atypical cell adhesion molecule that, based on its structure, cannot be grouped in the known cell adhesion family groups of cadherins, selectins, integrins and immunoglobulin superfamily (1).

EpCAM was originally identified as highly overexpressed in various carcinomas and consequently, has for many years been evaluated mainly as a target for anti-carcinoma therapy (2-4) (for review see 5-6). However, from these initial studies research on EpCAM has progressed to studies dedicated to its role in normal cellular behavior, which has yielded interesting new insights in EpCAM biology (for review see 1). It has by now been well established that EpCAM is also expressed in developing and normal, mature epithelia,

where it participates not only in cell adhesion, but also in proliferation, migration and differentiation (1,7-11). All of these processes are known to be fundamental for correct execution of morphogenesis, including embryo- and organogenesis, as well as tissue regeneration. Indeed, EpCAM was already proposed as a morphoregulatory molecule in the late 1990s (9,12). De Boer *et al*, identified that EpCAM was dynamically expressed in adult, normal, regenerating, metaplastic, and neoplastic liver, which together led them to hypothesize that EpCAM was associated with liver development (12). The hypothesis that EpCAM is a morphoregulatory protein is in line with the expression pattern of the rat homologue of EpCAM during rat development (13). Moreover, it is in line with the fact that addition of an anti-EpCAM antibody inhibits the differentiation of fetal pancreatic cells into pancreatic epithelial cells (11).

Embryonic development is one of the most complex biological phenomena that depends on the appropriate expression and synchronized interactions of a plethora of proteins. Of particular interest in this respect is the diverse family of cell adhesion molecules, of which many members have been shown to be critically involved in the correct execution of embryonic development, for instance the cadherins. This central role for cell adhesion is not surprising, since cell-cell interactions underlie many of the processes during embryonic development. For example, cell-cell interactions are required for germ cell survival as well as for cellular migration in embryonic and adult mice. In this review, we will discuss the current evidence that establishes EpCAM as a protein involved in morphogenesis.

3. EpCAM IN EARLY EMBRYOGENESIS

EpCAM is expressed from the earliest developmental stages. For instance, EpCAM is already present at the two cell stage and the morula stage (13). This is particularly interesting, since these early stages, do not contain epithelial cells yet. The morula is an early stage of embryonic development consisting of so-called blastomeres; cells that are not defined to a certain type of tissue. Blastomers may be considered as “precursor cells”, because they give rise to all cell types needed to build the mature organism, including epithelia. Thus, in contrast to its expression in adults the expression of EpCAM is not restricted to epithelia in early developmental stages. Interestingly, not all the cells in morula express EpCAM, whereas cells that do express EpCAM demonstrate a large variety in expression level (13).

During the next stage of embryogenesis the morula transforms into the so-called blastocyst, which consists of an inner cell mass, the trophoblast and the zona pellucida (14). Cells of both the inner cell mass and the trophoblast express EpCAM at a high level, whereas cells of the zona pellucida show a weaker expression of EpCAM. Similarly, we observed a different distribution and expression pattern of EpCAM within colonies of embryoid bodies (1).

The reasons for the differences in expression level and pattern in morula, blastocysts and in embryoid bodies are not clear. However, a common feature in all of the cells of these stages is the capability to give rise to different cell types and, ultimately, to different tissues and organs. Thus, expression of EpCAM in cells of these early developmental structures may be related to the target tissue/organ that will be formed. Similarly, cells that express EpCAM at these stages may already be precursors for epithelial cells, whereas cells that do not express EpCAM may be precursors of cells that will form non-epithelial tissues.

Another alternative explanation for the variable expression of EpCAM may lie in he possibility that cells of morula, blastocysts and embryoid bodies can be at different stages of differentiation. In this respect, expression of EpCAM was already proposed to be influenced by the differentiation stage of a cell (1). Since these early stages of development undergo intensive differentiation, distinct stages of differentiation can be observed at the same time, ranging from undifferentiated and initial stages of development to advanced or terminal stages of differentiation. Consequently, certain cells will share features in common with undifferentiated pluripotent cells, whereas other more differentiated cells will be more or less reminiscent to terminally differentiated cells, such as keratinocytes. Such distinct differentiation stages are characterized by expression or absence of various differentiation stage-specific markers. Thus, differentiation status of the cells may determine the presence and level of expression of EpCAM in morula, blastocysts, and embryoid bodies.

Reversely, EpCAM might be an active regulator of cell differentiation. Circumstantial evidence for such a role comes from ectopic overexpression of EpCAM, which induces redifferentiation in terminally differentiated cells, such as keratynocytes (7,8). However, the debate on EpCAM as active regulator of differentiation or as a ”passive” player in this process is still wide open.

At the following stage of embryonic development three embryonic germ layers are formed, namely the endoderm, the ectoderm and the mesoderm. Of these three layers, both the endoderm and ectoderm express EpCAM at the 8^{th} and 9^{th} day embryogenesis in rat (13). Mesodermal cells do not express EpCAM at that stage, but at later stages, i.e. 11.5 days of embryogenesis, mesoderm-derived epithelial cells do express EpCAM. Together, this suggests the presence of a very precise regulatory mechanism controlling both the spatial and temporal expression of EpCAM expression at early embryonic stages.

EpCAM has also been found in migrating embryonic and neonatal germ cells, whereas, terminally differentiated germ cells in adult mice cease to express EpCAM (15). Also rodent embryonic stem cells (ES cells) produce EpCAM (personal observation by M. Trzpis and (13,15)). Although the reason for this early expression is unknown, it seems to be a prerequisite for survival since attempts to knock-out EpCAM in ES-cells resulted in

lethality (S. Litvinov, personal communication P. McLaughlin). Since EpCAM mediates cell-cell adhesion, Anderson *et al*, investigated whether the ectopic expression of EpCAM in fibroblasts, used as feeder cells for ES cells, would influence ES cell morphology, for instance, by increasing the adhesion between the ES cells and the fibroblast monolayer (15). However, no obvious effect on the morphology and adhesiveness of the ES cells grown on EpCAM positive fibroblasts was observed. One possible interesting explanation for this lack of effect of EpCAM overexpression in fibroblast may lie in the fact that EpCAM expression in certain circumstances seems to prevent cell-cell adhesion (1).

In summary, EpCAM expression is detected already at the earliest stages where no epithelial cells are present yet. At these early stages, the expression of EpCAM is diverse, possibly reflecting different stages of cell differentiation or the presence of EpCAM within population of cells that will form different tissues. Moreover, EpCAM expression appears to be pivotal for ES cell survival.

4. EpCAM IN ORGANOGENESIS

Tarmann *et al* were the first to analyze the expression pattern of EpCAM during organogenesis in developing rat. They reported the very early expression of EpCAM as well as the epithelia-specific expression of EpCAM during complete embryogenesis (13). Several other articles have been dedicated to the possible involvement of EpCAM in organogenesis; most of which are descriptive and thus provide knowledge about the dynamics of EpCAM expression during organ formation. In the following section, we will summarize the evidence for the involvement of EpCAM in development of lung, kidney and pancreatic.

4.1. EpCAM expression in developing lung

Research suggesting that EpCAM is involved in human lung development was presented by Kasper *et al* (16). In their article, Kasper *et al* analyzed the expression of EpCAM in parallel with E-cadherin, since E-Cadherin has an established function in organogenesis (17,18). The expression of EpCAM was detected in developing lung at its earliest developmental stages and was sustained in mature epithelial cells. In fetal and adult pulmonary epithelia no differences between the expression pattern of EpCAM and that of E-cadherin were found. This is a surprising finding, since E-cadherin adhesion complexes are typical for terminally differentiated cells, whereas EpCAM is typically absent on terminally differentiated cells. Interestingly, the formation of E-cadherin mediated junctions inversely correlates with EpCAM expression (19). Moreover, EpCAM has been shown to abrogate E-cadherin adhesion complexes, as well as N-cadherin complexes, by disrupting the connection between α-catenin and the actin cytoskeleton (19,20). A recent article by Winter *et al*, suggests that this disassembly of cadherin complexes by EpCAM is related to the activation of PI3K signaling (20).

4.2. EpCAM expression in developing kidney

In our recent article, we demonstrated that EpCAM is present in renal epithelia at already the first day of kidney formation and remains present in renal epithelia till the end of nephrogenesis in the mature kidney (Trzpis *et al*, accepted by Nephron, 2007). Interestingly, EpCAM expression is not always restricted to only epithelial cells during kidney development. Comma and S-shaped bodies that consist of precursor cells from which renal epithelia, but also renal mesangial cells develop, also express EpCAM (Trzpis *et al*, 2007, accepted by Nephron). These findings are reminiscent of the expression of EpCAM in the earliest developmental stages, as described above, in which EpCAM expression was detected in precursor cells already at the 2-cell stage and the morula stage.

As for these early stages, the reason for the presence of EpCAM in these S- and comma shaped bodies is unclear. However, again, based on the properties ascribed to EpCAM, one can anticipate that its presence is associated with migration and differentiation of cells of S- and comma shaped bodies. Moreover, EpCAM mediated cell-cell adhesion is weaker than attachment mediated by for instance tight junctions, which may be profitable during cell migration.

Furthermore, podocytes, which are terminally differentiated epithelial cells, do not express EpCAM, which is in line with the hypothesis that EpCAM expression is influenced by the differentiation stage of cells.

Interestingly, the expression level of EpCAM varies markedly along the developing renal structures at each of the respective developmental stages analyzed, as well as along the mature nephron. In some structures expression is very low, for instance, in S- and comma-shaped bodies in the developing kidney and in the proximal tubules in the mature kidney. In other structures, such as the ureteric buds in the embryonic kidney, collecting ducts and distal tubules in adult kidney, expression level of EpCAM is very prominent. Thus, although all the renal epithelia express EpCAM, the expression pattern is dynamic and not homogenous. It is tempting to speculate that the exact level of expression of EpCAM may not only depend on the developmental stage, but also on the function assigned to the particular structure along the nephron.

4.3. EpCAM expression in developing pancreas

Elegant evidence for a role of EpCAM in pancreatic organogenesis was presented by Cirulli *et al*[11]. In agreement with our findings in kidney development, they observed a highly dynamic expression of EpCAM in developing pancreas; with the highest expression level of EpCAM being characteristic for developing islet-like cell clusters budding from the ductal epithelium. In contrast, the adult pancreas expressed low levels of EpCAM in islet cells but high level of EpCAM in ducts.

Interestingly, adult ductal cells have recently been proposed to be pancreatic stem cells (21). In light of this hypothesis, EpCAM would be expressed not only by

embryonic stem cells, as mentioned above, but also by adult stem cells in the pancreas. The presence of EpCAM in adult stem cells has also been reported for adult mammary glands stem cells (22). This stem cell expression of EpCAM might be important considering the association of EpCAM with tissue regeneration, as proposed by de Boer *et al* (5).

In this respect, it is interesting that expression of EpCAM has recently been shown to be a marker of human colorectal cancer stem cells (23). Dalerba *et al*. showed that the ability of colorectal tumor cells to engraft *in vivo* in immunodeficient mice was restricted to a subpopulation of cells highly positive for EpCAM and positive for CD44. In contrast, cells expressing low levels of EpCAM were unable to engraft. Interestingly, the xenografts formed by engrafted EpCAM-positive stem cells displayed the full spectrum of heterogeneity found in the original tumor. These experiments lend support for an important contributing role of EpCAM in colorectal cancer development and yield valuable insight into the function of EpCAM in cancer stem cells. It will be interesting to learn whether these findings can be extrapolated to a role for EpCAM in normal tissue stem cells, such as adult ductal cells and adult mammary gland stem cells.

Further *in vitro* evidence for a role of EpCAM in developing pancreas was obtained by Cirulli *et al* by subjecting fetal pancreatic epithelial cells to conditions that promote epithelial cell proliferation and growth, which resulted in an upregulation of the expression of EpCAM (11). In contrast, transplantation of undifferentiated fetal pancreatic epithelial cells to nude mice, leading to their progressive differentiation, resulted in significant downregulation of EpCAM expression. In addition, treatment of fetal pancreatic cells with a monoclonal anti-EpCAM antibody, thereby blocking EpCAM, resulted in the inhibition of cell adhesiveness, leading to a concomitant increase in production of insulin and glucagon. Apparently, inhibition of EpCAM in fetal pancreatic cells shifts the balance towards endocrine differentiation.

Taken together, the above described studies clearly show the association of expression of EpCAM with progression to epithelial tissues/organ development. The most striking observation of these studies is that, although EpCAM is constantly expressed in epithelia, the expression pattern is not homogeneous but differs between different developmental stages and depending on differentiation status of the cells.

5. CONCLUDING REMARKS

With the complexity of diverse groups of molecules participating in morphogenesis taken into account, it seems that one of the essential predetermining factors would be the expression pattern of a protein at a particular stage of development. Based on this assumption, EpCAM with its restricted spatial and temporal expression is relevant to morphogenesis. Further support for the role of EpCAM in morphogenesis comes from mechanistic studies showing that EpCAM expression is indeed associated with cell proliferation and differentiation during organogenesis (7-9,11,24).

An obvious and intriguing question that arises from these initial studies is what exactly the mechanism is that links EpCAM with morphogenesis. To date, this question is still largely unanswered and thus promises to be an interesting area of research in the coming years. However, one can make some predictions on the role of EpCAM based on the current largely descriptive knowledge. For instance, based on the expression levels of EpCAM during morphogenesis, it is reasonable to assume that its function is not really specific for a given stage of nephrogenesis, but rather important during the whole organogenic process. A similar role has been reported for e.g. cadherins during organogenesis.

Despite the fact that the expression of EpCAM is not stage specific, a well-orchestrated and coordinated (direct or indirect) interplay of EpCAM with other proteins, which might be differentially expressed during the same time frame, is most likely crucial for successful morphogenesis. Indeed, a diverse panel of proteins is known to interact with EpCAM. Thus it is reasonable to assume that EpCAM does not work by itself but its actions are supported or even determined by the environment of interacting proteins, as recently reviewed (1). In this respect, EpCAM has been shown to interact with claudin-7, a protein involved in tight junction formation (25). Recent evidence suggests that tight junctions participate in signal transduction mechanisms that regulate epithelial cell proliferation, differentiation and morphogenesis (26). Therefore, it would be of particular interest to identify the mechanism and consequence of EpCAM/claudin-7 interaction in relation to morphogenesis.

In addition, via its direct interaction with claudin-7, EpCAM also indirectly associates with CD44 variant isoforms and tetraspanins in colon cancer cells, where these complexes were found to promote colorectal cancer progression (27). It will be interesting to see whether similar complexes can be identified in non-carcinoma cells, i.e. during morphogenesis to further evaluate role of EpCAM during this process.

Future research on EpCAM in relation to organogenesis is likely to provide an answer to the question posed above, namely what exactly is the role of EpCAM in morphogenesis. One possible method of obtaining functional evidence for the role of EpCAM is the use of blocking anti-EpCAM antibodies, as for instance successfully applied by Cirulli *et al* to pancreatic development *in vitro* (11). An additional and promising approach is the development of a (conditional) knock-out animal model of EpCAM. Such models have already been successfully applied to e.g. E-cadherin by Gaetano Calì *et al*, who conditionally inactivated the E-cadherin gene in thyroid follicular cells of mouse embryo to unravel its role in thyroid development (28).

Unfortunately, there is considerable redundancy between various CAMs, which in itself is not surprising in

light of their crucial function in embryonic development. As a result, the ultimate consequence of knocking-down a single CAM may be limited. Interestingly, since EpCAM is an atypical cell adhesion molecule without obvious redundancy in regard to the structural resemblances to other CAMs, it will be interesting and certainly worthwhile to determine what the consequence of knocking-out EpCAM will be for organogenesis. At the same time, it is reasonable to assume that nature has provided for at least one backup system in the absence of EpCAM. Therefore, it is of pivotal importance to further elucidate the molecular mechanism of EpCAM biology, particularly in relation to its multiple binding partners.

In conclusion, research on EpCAM in organogenesis has provided compelling evidence for a fundamental role of EpCAM in this process. Research focused on determining the functional consequences of EpCAM at each of the different stages of embryonic development will provide new insights into the biology of this pleiotropic molecule.

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