The outcome of liver injury is dictated by the effectiveness of repair. Successful repair (i.e., regeneration) results in replacement of dead epithelial cells with healthy epithelial cells, and reconstructs normal hepatic structure and function. Liver regeneration is known to involve replication of surviving mature hepatocytes and bile duct cells. This review discusses recent evidence for other mechanisms that might also replace dead hepatic epithelial cells and repair liver damage, particularly during chronic injury. According to this theory, certain epithelial cells in developing livers and/or injured adult livers undergo epithelial-to-mesenchymal transition (EMT) and move into the hepatic mesenchyme where they exhibit fibroblastic features. Some of these epithelia-derived mesenchymal cells, however, may be capable of undergoing subsequent mesenchymal-to-epithelial transition (MET), reverting to epithelial cells that ultimately become hepatocytes or cholangiocytes. Although these concepts remain to be proven, the theory predicts that the balance between EMT and MET modulates the outcome of chronic liver injury. When EMT activity outstrips MET, repair is mainly fibrogenic, causing liver fibrosis. Conversely, predominance of MET favors more normal liver regeneration. In this review, we summarize evidence that certain resident liver cells are capable of EMTs \textit{in vitro} and during chronic liver injury. (HEPATOLOGY 2009;50:2007-2013.)

Similar to the skin, intestine, lung, and glandular tissues like the pancreas, the adult liver is comprised largely of epithelial cells and mesenchymal cells. In all of these organs the ultimate outcome of epithelial injury is dictated by repair. Successful liver repair results in replacement of dead or damaged hepatic epithelial cells with healthy new epithelial cells, i.e., liver regeneration. Regenerative responses differ depending on the severity and chronicity of liver injury. For example, residual mature hepatocytes and cholangiocytes proliferate to restore liver mass after acute partial hepatectomy, whereas liver progenitors are involved in the repair of chronically injured livers. Repair of chronic liver injury also variably involves changes in mesenchymal cells. Presumably, alterations in hepatic “stromal” cells in some way contribute to epithelial repair. However, they may also lead to hepatic inflammation, vascular remodeling, and fibrosis, and result in hepatic architectural distortion and liver dysfunction, eventually culminating in cirrhosis. Therefore, efforts have focused on understanding the mechanisms that control potentially “fibrogenic” repair. The purpose of this review is to summarize evidence for and against the possibility that fibrogenic repair involves epithelial-to-mesenchymal transitions (EMT) and mesenchymal-to-epithelial transitions (MET) of resident liver cells.

Definitions

Epithelial cells are adherent cells that closely attach to each other, forming coherent layers in which cells exhibit apico-basal polarity. Mesenchymal cells, in contrast, are nonpolarized cells, capable of moving as individual cells because they lack intercellular connections. EMT describes the process by which cells gradually lose typical epithelial characteristics and acquire mesenchymal traits. MET refers to the reverse process. It is important to emphasize that EMT/MET refer to changes in cell shape and adhesive properties. Cell fate (lineage) is specified by other mechanisms. Hence, EMT/MET are merely manifestations of the inherent plasticity of cells.

Key epithelial features that are eventually lost during EMT include typical epithelial expression and distribution of proteins that mediate cell-cell and cell-matrix con-
tacts, as well as the cytoskeletal organization that is responsible for normal epithelial polarity. Key mesenchymal characteristics that are ultimately gained during EMT include the ability to migrate and invade the surrounding matrix. This migratory/invasive phenotype requires induction of mesenchymal filaments, cytoskeletal rearrangements, and increased production of factors that degrade extracellular matrix, as well as new matrix molecules themselves. Such global alterations in cellular phenotype do not occur simultaneously. Rather, completion of EMT (or its reversal) requires a carefully orchestrated series of events that eventually lead to widespread changes in gene expression. This is regulated both at the level of gene transcription and via various posttranscriptional mechanisms.

**Situations Associated with EMTs**

EMT/MET occur when tissues are being built or remodeled. Hence, EMT/MET are involved in (1) embryogenesis/development, (2) wound healing/tissue regeneration/organ fibrosis, and (3) neoplasia. Because the context and consequences of EMT/MET differ in these three settings, consensus is emerging that EMTs are best classified into three different biological subtypes based on the biological context in which they occur. A detailed description of similarities and differences in the three subtypes of EMTs is provided in recent review articles. Briefly, type 1 EMTs occur during implantation, embryogenesis, and organ development. Among other outcomes, type 1 EMT generates mesodermal and endodermal mesenchyme that then undergoes MET to generate secondary epithelia that, in turn, undergo further rounds of EMT/MET to form various organs. Type 1 EMT does not cause fibrosis. In contrast, fibrosis is a potential outcome of type 2 EMT. The latter generally begins as a repair-associated event in adult tissues. Type 2 EMT is associated with inflammation and generally abates when inflammation subsides, presumably because superfluous fibroblastic cells that emerged during the process undergo apoptosis. However, when injury and inflammation persist, type 2 EMT generates fibroblastic cells that accumulate and cause progressive fibrosis, eventually in organ destruction. Type 3 EMTs occur as a result of genetic and epigenetic changes in cancer cells and promote invasion and spread of tumor cells, as well as subsequent emergence of metastatic tumor foci at sites distant from the primary tumor. Type 3 EMTs resemble type 1 EMTs in that generation of epithelia, rather than fibrosis, is typically the ultimate outcome. Although these three classes of EMTs represent distinct biological processes and, therefore, have various unique features, it has been proposed that “a common set of genetic and biochemical elements appears to underlie, and thus enable, these outwardly diverse phenotypic programs.” Further research is needed to evaluate this concept, particularly in various adult tissues where it remains debated if (and to what extent) EMT occurs during chronic degenerative/fibrosing disorders.

**Regulation of EMT**

Most of the existing fundamental knowledge about EMT regulation has been generated by studying cultures of malignant and nonmalignant cells because EMT is relatively easy to induce in cultured epithelial cells. Additional knowledge has been gained by tracking and manipulating organogenesis during fetal development. A detailed discussion of this research is beyond the scope of this review. It is important to emphasize, however, that results in cell culture systems may not perfectly recapitulate the cues that control EMTs in intact tissues. In addition, unique modulatory mechanisms are likely to influence EMT depending on the biological context (i.e., development versus neoplasia versus adult repair) and specific cell type (e.g., normal progenitor versus malignant transformed cell versus mature epithelial cells) in which EMT occurs. Existing evidence also suggests that types 1 and 3 EMT might be more similar to each other than to type 2 EMT, which occurs mainly in injured/inflamed adult tissues. Suffice it to say, however, that the work in cultured cells and developing embryos has led to the identification of common matrix molecules and a repertoire of soluble factors that are capable of triggering EMT in certain epithelial cell types. Activation of specific receptors by transforming growth factor-beta (TGF-β1) has been shown to provoke EMT in many types of epithelial cells in culture. Hence, TGF-β1 is generally considered one of the master positive regulators of EMT. Conversely, another TGF-β family member, bone morphogenetic protein 7 (BMP-7), is the prototypical negative regulator of EMT because it generally, although not always, opposes the EMT promoting actions of TGF-β receptor activation. Experimental manipulation of signaling events downstream from TGF-β1 and BMP-7 receptors has, therefore, been used to tease out mechanisms that mediate distinct processes that occur during EMT, such as disruption of cell-cell adherence, loss of apico-basal polarity, matrix remodeling, and migration. As a result, it has become evident that although overlapping mechanisms mediate many of the different events that transpire as cells lose epithelial characteristics and gain mesenchymal features, distinct signals also regulate each of the different processes. Consequently, different aspects of EMT generally occur sequentially, with inhibition of cell-cell contact occurring before cytoskeletal
rearrangement and acquisition of a motile/invasive phenotype. Thus, at any given moment, individual cells in a culture or tissue may be at different stages of EMT, depending on which signals have already been launched, and which signals have not yet been initiated. This heterogeneity complicates efforts to identify cells that are undergoing EMT, particularly in intact tissues. Efforts to “simplify” analysis by focusing attention on matrix-producing cells introduce bias, however, because many types of fibroblastic cells are capable of generating matrix molecules, and matrix production is not an obligate feature of EMT. Moreover, it remains to be determined to what (if any) extent EMT contributes to adult organ fibrosis, although type 2 EMT is defined by its association with this process.

**Challenges to Identifying Cells that are Undergoing EMT**

Cells that are in the midst of EMT are sometimes referred to as “transitioning cells” or cells that have undergone “partial EMT.” Concomitant expression of epithelial and mesenchymal markers is often used to identify cells that are undergoing EMT. However, it is important to recognize that EMT may be under way in epithelial cells that have not yet fully activated expression of mesenchymal genes. The phenotype of mesenchymal cells is also dynamic. Hence, not every mesenchymal marker is expressed concurrently, and this complicates efforts to identify a cell as being (or not being) mesenchymal. The issue is further confounded by evidence that EMT may be reversible by a process termed mesenchymal-to-epithelial transition (MET). MET presumably involves “reverse” sequential silencing of the mechanisms that led to EMT, thereby permitting a mesenchymal-type cell that was derived from an epithelial cell to gradually reacquire its epithelial phenotype. The possibility that many cells are capable of undergoing both EMT and MET provides further evidence for the inherent plasticity of cells, but complicates efforts to prove either the origin or fate of individual fibroblastic cells, particularly in intact tissues. A consensus panel of EMT experts recently developed an array of parameters that are useful for “diagnosing” EMT in situations where cellular lineage-tracing (see below) is not possible, including analysis of human tissue samples. The likelihood of EMT increases with the number of individual criteria that are satisfied.

**Evidence that Certain Adult Liver Cell Types are Capable of EMTs**

Three types of adult liver cells, hepatocytes, cholangiocytes, and hepatic stellate cells (HSC), have been shown to undergo epithelial-mesenchymal transitions (i.e., EMT or MET) in culture. Several groups have demonstrated that treating primary rat hepatocytes or hepatocyte cell lines with sublethal doses of TGF-β causes them to down-regulate expression of epithelial genes, such as albumin, up-regulate expression of mesenchymal genes, including α-smooth muscle actin (α-sma), collagen, and fibroblast-specific protein 1 (FSP-1), and/or to acquire a migratory phenotype. Primary hepatocytes from rats with carbon tetrachloride (CCL4)-induced cirrhosis exhibit characteristics of mesenchymal cells. Hence, there is solid experimental evidence that hepatocytes can be induced to undergo EMT in culture, and some data that a similar process may occur during conditions that promote liver fibrosis in vivo.

Omenetti et al. reported that treating an immature cholangiocyte line with conditioned medium from myofibroblastic HSC (MF-HSC) caused the cholangiocytes to undergo complete EMT (i.e., to repress expression of epithelial genes, induce expression of mesenchymal genes, and acquire a migratory phenotype). In addition, they demonstrated that primary cholangiocytes from rats with biliary fibrosis coexpressed epithelial and mesenchymal markers, a characteristic of cells that are undergoing EMT. Rygiel et al. also documented coexpression of epithelial and mesenchymal markers in intrahepatic biliary epithelial cells in human tissues, and reported that cultured primary human cholangiocytes induced mesenchymal markers and became highly motile when treated with TGF-β. Finally, colocalization of CK19 (a marker of bile ductular cells) and various mesenchymal proteins was demonstrated by Diaz et al. in their studies of biliary atresia and several other liver diseases that are associated with bile ductular proliferation. Hence, there is strong evidence that, like hepatocytes, bile ductular cells are capable of EMT in vitro, and perhaps, in vivo.

The concept that cells that are involved in ductular reactions during chronic liver injury are capable of EMT is intriguing because subpopulations of these cells are thought to comprise liver epithelial progenitors. Yovchev et al. recently reported coexpression of epithelial and mesenchymal markers in liver epithelial progenitors (oval cells) that they purified from rats that had been treated to increase liver progenitors. The investigators went on to prove that these transitional cells were true hepatic progenitors by transplanting them into rats with injured livers and demonstrating hepatic repopulation. That liver progenitors are capable of undergoing EMT’s is further supported by evidence that progenitor cells from fetal livers undergo EMT/MET. Hepatic stellate cells might also be capable of METs. Recent publications from two independent groups suggest that HSCs are derived from submesothelial cells dur-
Evidence for EMT During Liver Injury

Determining whether or not EMT occurs in situ, and how significant this process might be to outcomes of liver injury (e.g., regeneration or fibrosis), is inherently difficult. Unlike development or carcinogenesis, during which large populations of cells typically undergo relatively synchronous EMT, chronic epithelial degeneration is thought to provoke patchy EMTs that involve relatively small numbers of cells. Thus, assessment of EMT in adult liver repair has generally been addressed by immunohistochemistry. However, technical considerations limit the numbers of cellular proteins that can be demonstrated in any given cell at any point in time. Therefore, it is simply not feasible to obtain a “snapshot” that captures global changes in the phenotype of individual cells using this approach. Moreover, even when staining suggests coexpression of individual epithelial and mesenchymal markers, it is often difficult to resolve whether or not the seemingly colocalized markers are actually expressed by one cell, as opposed to the possibility that one of the markers is being expressed by another adjacent/adenherent cell. The latter is virtually impossible to exclude when serial sections are stained individually to generate photomicrographs that are then “overlaid” on each other to estimate marker coexpression. Finally, without time-lapse photography, even superb immunohistochemistry is incapable of capturing cell movement, and the latter is generally considered to be a critical proof-of-concept that a cell has undergone complete EMT.

Fate-mapping (also termed lineage-tracing) is another approach that has been used to track transitions in cell phenotype, including EMT/MET. This strategy uses cell-type-specific activation of gene regulatory elements to generate permanently expressed markers (e.g., LacZ) that specifically identify all of the different progeny of that cell type. For example, transgenic mice have been generated in which cis-acting elements that control albumin gene expression were used to drive expression of Cre-recombinase. In such mice, only cells that activated albumin gene transcription produced Cre-recombinase. Cre-recombinase cleaves loxP sites, removing “floxed” segments of DNA that are flanked by engineered loxP sites. Breeding such albumin-cre mice with floxStopRepressor floxLacZ transgenic mice resulted in double transgenic mice in which the role of hepatocyte EMT in CCl4-induced hepatic fibrosis. A detailed description of their work is justified because it is the first of only three studies that have attempted to use fate-mapping to monitor cellular transitions during adult liver injury/repair. The authors tracked the accumulation of fibroblastic cells that expressed FSP-1, a marker of fibroblastoid cells that are generated by EMT during renal models of fibrosis.
mained what proportion of these EMT-derived fibroblastic cells were LacZ-expressing (i.e., β-gal-positive). In healthy control livers, only a few FSP (+)-fibroblastic cells were noted, predominately around terminal hepatic venules and within portal tracts. However, during CCl₄ treatment FSP (+)-fibroblastic cells accumulated in areas of collagen deposition. Cells that expressed α-sma also accumulated during liver fibrosis. The latter are generally considered myofibroblasts that are generated mostly from Q-HSC.3 Interestingly, populations of α-sma-expressing cells and FSP (+)-cells were largely discrete, with each cell population increasing as fibrosis progressed, such that each cell type comprised ≈10%-15% of the liver 6 weeks post-CCl₄ treatment. Only about 10% of the fibroblastic cells coexpressed both markers at that timepoint. In contrast, almost half of the FSP-expressing fibroblastic cells coexpressed β-gal, leading to the conclusion that most of the EMT-derived fibroblastic cells were derived from hepatocytes. These findings have been widely cited and are generally considered to provide the most definitive proof of the concept that hepatocyte EMT contributes to liver fibrosis.

However, like all good research, this study generates as many questions as it resolves. First, it is notable that over half of the FSP (+)-fibroblastic cells in fibrotic livers did not exhibit β-gal activity. Therefore, these cells were not derived from mature hepatocytes that had activated albumin transcription. Indeed, only about 70% of the hepatocytes in the healthy Alb-Cre-LacZ mice exhibited β-gal activity pretreatment, suggesting that progeny of almost one-third of the hepatocytic cells would not be identified by β-gal staining. Although it is conceivable that technical artifacts account for the apparent lack of β-gal expression in sizeable subpopulations of hepatocytic and fibroblastic cells in this study, other explanations also merit consideration, particularly given strong in vitro evidence that other types of liver cells are capable of EMT/MET. The latter suggests that cholangiocytes and/or HSC might have undergone epithelial-mesenchymal transitions (EMT and/or MET) to generate β-gal-negative fibroblastic cells and/or hepatocytic cells in Alb-Cre/LacZ transgenic mice. Unfortunately, information to resolve this issue is lacking. It was not specified if ductular-appearing cells expressed FSP-1 in CCl₄-treated Alb-Cre/LacZ mice, although cholangiocyte expression of FSP-1 has been demonstrated in mice and humans with biliary-type fibrosis.19,22 Also unknown is whether β-gal activity was demonstrated in any of the α-sma-expressing cells. Others have demonstrated that hepatocytes can express α-sma when they are induced to undergo EMT in culture,15 and shown that α-sma (+) MF-HSC can be induced to express markers of immature and mature hepatocytes.31,32 Finally, because staining was not done to prove that β-gal (+) fibroblastic cells were actually producing matrix molecules, it remains unclear whether these EMT-derived cells directly contributed matrix deposition during liver fibrosis. Thus, even this sophisticated fate-mapping approach has limitations that preclude definitive assignment of the origin (or fate) of various fibroblastic cells during liver fibrogenesis, or their precise roles in liver repair.

The second attempt to use fate-mapping to track transitioning cells during adult liver injury also relied on cell-specific deletion of the floxStopRepressor cassette. In this case, floxStopRepressorflox green fluorescent protein (GFP) transgenic mice were bred with glial fibrillary acidic protein (GFAP)-Cre mice. The resultant double transgenic, GFAP-Cre/GFP mice expressed Cre-recombinase exclusively in cells that activated transcription of GFAP. GFAP is a marker of HSC in adult liver.3 Thus, these mice were designed to track the progeny of HSC in order to determine if HSC undergo MET to generate mature liver epithelial cells after diet-induced liver injury.36 In the livers of healthy adult GFAP-Cre/GFP mice, stellate-appearing sinusoidal cells expressed GFAP, Cre-recombinase, and GFP; each of these genes was also expressed in freshly isolated Q-HSC; when Q-HSC were cultured, the myofibroblastic progeny remained GFP (+) despite having down-regulated expression of GFAP and Cre-recombinase. Surprisingly, however, many bile ductular cells also expressed GFAP, Cre-recombinase, and GFP in the healthy adult mice. The latter confounded efforts to interpret the dramatic findings that were noted in these mice during and after liver injury. Namely, roughly one-third of the mature-appearing albumin (+) hepatocytes, and virtually all of the ductular cells in the regenerating livers of these mice expressed the fate-mapping marker, but it was impossible to determine if such cells were derived from HSC, ductular cells, or some other GFAP-expressing progenitor cell. Nevertheless, these data raise the intriguing possibility that hepatocytes, cholangiocytes, and HSC are derived from a common progenitor that is capable of EMT/MET during certain types of liver injury.

The third fate-mapping study that investigated cell transitions during liver injury was published by Sackett et al.36 FloxStopRepressorfloxLacZ transgenic mice were bred with transgenic mice that expressed Cre-recombinase under the control of regulatory elements for Foxl1, a gene that is expressed in mesenchymal progenitor cells in the intestine.37 Thus, all Foxl1-expressing cells and their progeny were expected to exhibit β-gal activity in Foxl1-cre/LacZ mice. These mice were then subjected to bile duct ligation (BDL) or treatment with a hepatotoxin that promotes oval cell accumulation. In healthy mice, β-gal-
expressing cells were localized in portal tract ductular structures, and some β-gal (+)-ductular cells coexpressed CK19, a marker of mature cholangiocytes. After both types of liver injury, Foxl1-expressing cells generated progeny that differentiated mainly along the biliary lineage, although small numbers of β-gal (+) hepatocytes were also noted. β-Gal did not colocalize with markers of portal fibroblasts (elastin), Q-HSC (desmin), or myofibroblasts (α-sm), suggesting that neither Foxl1-expressing progenitors nor their progeny acquired a mesenchymal phenotype at the timepoints examined. However, given the dynamic nature of EMT/MET, it is impossible to know if such processes might have occurred in Foxl1-expressing cells or their progeny at other times. Also, these findings do not exclude EMT/MET in non-Foxl1-derived cells.

Summary

Epithelial-mesenchymal transitions (EMT/MET) are known to occur when tissues are constructed during embryogenesis/development. They are also thought to occur during adult tissue remodeling responses, including carcinogenesis and fibrosis. During culture, several resident adult liver cells appear capable of undergoing EMT and/or MET, raising the possibility that EMT/MET might be involved in liver regeneration. However, despite considerable effort to deploy state-of-the-art technology to determine if (and how) such phenotypic transitions influence the outcomes of liver injury, the issue remains quite confusing. The existing fate-mapping data that might prove to be helpful in resolving the role of EMT’s in adult liver repair was derived from three different transgenic mice, each of which likely marked distinct types of liver cells and their resultant progeny. Data interpretation is further confounded by the fact that the published studies used different models of injury and examined outcomes at different timepoints. Nevertheless, a few take-home messages have emerged. Two of the three studies (work in Alb-Cre/LacZ mice and GFAP-Cre/GFP mice) provide compelling in vivo evidence that EMT/MET does occur in certain types of adult liver injury, although the exact cell types that are capable of this response remain unclear. Also, when it occurs, EMT does appear to correlate with changes in hepatic matrix production/accumulation, although it has not yet been proved (or disproved) that the EMT-derived fibroblastic cells actually generate matrix. One of the three studies (work in GFAP-Cre/GFP mice) suggests that MET may have a significant role in hepatocyte regeneration. Despite the acknowledged technical limitations, there is also growing immunohistochemical evidence for EMT/MET in various human liver diseases, including primary biliary cirrhosis, biliary atresia, and alcoholic and nonalcoholic fatty liver disease.19,21,22 In addition, therapeutic manipulation of known EMT regulators has generally been demonstrated to influence liver regeneration and fibrosis in rodents. For example, supplementing BMP-7 inhibited liver fibrosis in CCl4-treated mice,10,38 and improved liver regeneration after partial hepatectomy,39 whereas inhibiting BMP-7 activity delayed normal, post-partial hepatectomy regeneration in mice.39 Likewise, pharmacological inhibition of cholangiocyte αvβ6 integrin, a receptor that is selectively induced in epithelial cells that are undergoing EMT, blocked biliary fibrosis in rodents.40 Coupled with strong in vitro data demonstrating that several types of cells in healthy adult liver are capable of undergoing EMT/MET,10,15-19,31,32 all of this information suggests a novel model for repair of chronically injured livers, in which the balance between EMT and MET dictate whether or not repair is fibrogenic (Fig. 1). Further research is needed to
evaluate this theory. The resultant knowledge may be important in designing novel diagnostic and therapeutic strategies to prevent and treat liver damage.

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