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Cytokeratins of the Liver and Intestine Epithelial Cells During Development and Disease

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1. Introduction

A large part of the cytoplasm of the cells consists of components forming cytoskeleton. The constituents of the cytoskeleton in epithelial cells are actin-containing microfilaments, tubulin-containing microtubules and intermediate size filaments. The intermediate filaments are called as cytokeratins (CK). Thus, cytokeratins are a family of many different filament-forming proteins (polypeptides) with specific physicochemical properties and are normal components of epithelial cell cytoskeleton. CK are expressed in various types of epithelia in different combinations. Cytokeratins account for about 80% of the total protein content in differentiated cells of stratified epithelia (Pekny and Lane 2007). In both human and murine stratified epidermis, CK account for 25–35% of the extracted proteins(Bowden, Quinlan et al. 1984). The expression of proteins forming intermediate filaments can change when epithelial cells develop into mesenchymal cells and vice versa(Moll, Moll et al. 1984). For example, during neural tube formation, CK-producing ectodermal cells change into vimentin-producing mesenchymal cells, whereas during the formation of renal tubules vimentin-producing mesenchymal cells change into CK-producing epithelial cells(Moll, et al. 1984). Different types of cytokeratins are distinguished according to various characteristics, such as physicochemical properties, or according to the cells and tissues that produce certain CK. In simple, non-stratified epithelia these proteins are different than those in stratified epithelia. Epithelial cells in simple as well as in stratified epithelia always synthesize particular CK on a regular basis. These cytokeratins are referred to as the primary keratins of epithelial cells, such as CK8/CK18 in simple epithelia (Pekny and Lane 2007) or CK5/CK14 in stratified(Moll, Franke et al. 1982). In addition or instead, these epithelial cells can also produce secondary CK, such as CK7/CK19 in simple epithelia or CK15 and CK6/CK16 in stratified epithelia.

During embryonic development of simple to stratified epithelia, different cytokeratins are expressed (Banksschlegel 1982). Cells of the single-layered precursor of the human epidermis produce the same types of CK that are characteristic of simple epithelia, namely CK8, CK18 and CK19 (Dale, Holbrook et al. 1985). With the onset of stratification, different cytokeratins are expressed in the basal and suprabasal layers, e.g. CK5 is produced instead of CK8. With the onset of keratinization, CK1 and CK10 are added to the cytoskeleton in the suprabasal cell layers. Around the same time, there is a change in the expression of certain

keratin genes, with large keratins being produced with the onset of keratinization, and smaller ones no longer being synthesized (Banksschlegel 1982).

In medical diagnosis, antibodies against various cytokeratins have been used to characterize a wide variety of epithelial tumors. For example immunohistochemical detection of cytokeratin can identify micrometastases, not detected by conventional hematoxylin and eosin staining, Also serum cytokeratins levels are widely used as markers of tumors of epithelial origin (Linder 2007).

2. Role of keratins

The main function of cytokeratins is to give mechanical strength to the epithelial cells. But importance of this function depends upon the cell type. The epithelial layer which is constantly exposed to mechanical stress like epidermis, this function is important but this function is not so much important in single layered epithelial cells of internal organs which are not exposed to much mechanical stress. In polarized epithelial cells like intestinal epithelial cells, keratins play the role to maintain the cell polarity (Owens and Lane 2003; Oriolo, Wald et al. 2007). CK are not evenly distributed throughout the cytoplasm. CK19 is most abundant at the apical end below microvilli. Defect in CK19 expression affects the polarity of the cell (Salas, Rodriguez et al. 1997). In rat intestine, staining of CK8 and CK21 is observed at the cell periphery of absorptive cells while staining of CK19 is observed at the central region (Habtezion, Toivola et al. 2011). Cytokeratin filaments are also important in intercellular context. They are attached to the desmosomes as well as hemi-desmosomes. Thus they help in cell-cell adhesion and also attachment of the epithelial cells with the underlining connective tissue. Besides this structural function CK also plays a role in transport of some membrane proteins (Coulombe, Tong et al. 2004; Zhou, Cadrin et al. 2006; Kim and Coulombe 2007). In CK8 null mice, it is observed that there is abnormality in the distribution of apical surface markers. Regional differences in the expression of syntaxin-3, intestinal alkaline phosphatase and CFTR chloride channel proteins were observed in small intestine of CK8 null animals (Oshima 2002). Role of keratins in cell signaling is also proposed. Simple epithelial keratin pair; CK8/CK18 interact with Fas and TNF-alpha receptors (Caulin, Ware et al. 2000; Oshima 2002; Paramio and Jorcano 2002). Cells deficient in CK8 and CK18 are more sensitive to TNF induced cell death (Inada, Izawa et al. 2001).

Role of CK in apoptosis is documented in many studies (Ku, Liao et al. 1997; Oshima 2002; Owens and Lane 2003). In apoptosis process, the pre-apoptotic event is the hyper phosphorylation of keratin filament. These CK are then degraded by caspase. Only type I CK are susceptible to caspase mediated proteolysis and not type II CK. Phosphorylated CK8/CK18 pair is the substrate for pro-caspase 3 and 9 (Lee, Schickling et al. 2002; Dinsdale, Lee et al. 2004). Breakdown of this keratin pair results in the collapse of cytoplasmic and nuclear cytoskeleton which leads to the condensation of chromatin, which is the hallmark of apoptosis process. Organized cell fragmentation during apoptosis is essential to prevent the induction of inflammatory response. Programmed destruction of CK network is essential for this. Defect in CK composition may affect the sensitivity of the cell to apoptosis which is proposed in case of colonic hyperplasia. But there are also some studies in which (Ku and Omary 2000) it is stated that hyper-

phosphorylation of CK does not make the cells susceptible to apoptosis. It only affects the dimer formation (Strnad, Windoffer et al. 2001).

At this point in time, the expression of cytokeratins during development of human liver and intestine need clarification and the functional importance of these proteins in liver and intestine diseases require updating. Furthermore, much is known now about the expression, assembly, and function of CK in keratinized epithelial cells, the main features being the tight coupling between CK pair switch and cell terminal differentiation (protection barrier) and the vital role of CK intermediate filaments in cell mechanical integrity. However, the picture about non-keratinizing epithelia, like the hepatic tissue, remains quite unclear. In this review we will address these issues and also highlight the role of CK in liver and intestinal diseases.

3. Cytokeratin expression during liver development and regeneration

During embryological development, around 8 gestational weeks (GW), bipotential hepatoblasts stream from the hepatic diverticulum, and differentiate into both hepatocytes and ductal plate cells. Human intrahepatic biliary system arises from the ductal plate, which is a double-layered cylindrical structure located at the interface between portal mesenchyme and primitive hepatocytes. Around 12 GW, the ductal plate gradually undergoes remodeling; some parts of the ductal plate disappear and other parts migrate into the portal mesenchyme. Around 20 GW, the migrated duct cells transform into immature bile ducts and peribiliary glands (Bateman and Hubscher 2010). Around postnatal 3 months, some immature peribiliary glands transform into pancreatic acinar cells. These embryological progenitor cells express a broad range of cytokeratins – CK8, CK18, CK19 and (transiently) CK14. Ductal plate cells continue to express CK8, CK18 and CK19 and at 20 weeks of gestation begin to express CK7. This immunophenotype is retained by mature bile ducts at birth. Developing hepatocytes express CK8 and CK18 but not CK7 or CK19 (Desmet, Vaneyken et al. 1990).

It is now believed that the role of progenitor cells in liver regeneration may have similarities to embryological liver development. Studies have attempted to define the nature and position of progenitor cells within the liver in a variety of ways. This has included study of animal models of liver diseases, embryological human livers in cell culture and *in vivo* (Nava, Westgren et al. 2005) (Nowak et al. 2005) and adult human livers in cell culture (Herrera, Bruno et al. 2006) (Khuu, Najimi et al. 2007) and *in vivo* (Chatzipantelis, Lazaris et al. 2006). In our own studies we demonstrated that *in vitro* expanded human fetal liver progenitor cells express CK18, CK8 and some CK19 (Figure 1). In fact, these double positive (positive for CK18 and CK19) later differentiate into cells expressing either only CK18 (hepatocytes) or only CK19 (bile duct cells-cholangiocytes). Interestingly, a cell type termed the 'oval' cell has been described as a putative hepatic stem cell in animal (especially rat) models. These cells appear in the portal and periportal regions of animal livers within a few days of liver injury and may express biliary markers such as CK7 and CK19 as well as hepatocyte markers such as pyruvate kinase isoenzyme L-PK, albumin and alpha-fetoprotein (AFP). They may also express other markers such as OV-6, an antibody raised in mice and recognizing epitopes within CK14 and CK19 in rats (Vessey and Hall 2001). Oval cells differentiate into hepatocytes via 'transitional' hepatocytes.

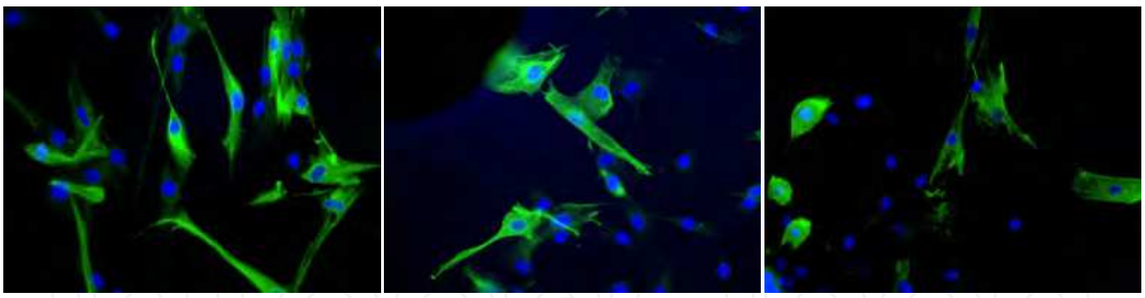

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Fig. 1. Immunofluorescence staining of in vitro expanded human fetal liver progenitor cells showing expression of (A) CK18 in almost all cells, while (B) CK8 and (C) CK19 expression was found only in some cells.

4. Distribution of cytoskeleton intermediate filaments during fetal hepatocyte differentiation

During fetal development, the construction of the liver parenchyma depends on the intricate relationship of intercellular contacts between epithelial cells and between epithelial and mesenchymal cells. In the early stages of fetal rat (Vassy, Rigaut et al. 1990) and human (Nava, Westgren et al. 2005) development, the liver is mainly a hematopoietic organ and hepatocytes represent fewer than 40% of all liver cells. In rats, at this time, cytokeratin filaments are scarce but are uniformly distributed inside the cytoplasm (Vassy, Irinopoulou et al. 1997). A coexpression of desmin and cytokeratin is found in some cells. Intercellular contacts between epithelial and mesenchymal cells are more numerous than between epithelial cells. Later in development, contacts between hepatocytes become more numerous and bile canaliculi become well developed. The density of cytokeratin filaments increases and appears to be very high near the bile canaliculi. In adult liver, hepatocytes are arranged in a "muralium simplex" architecture (one-cell-thick sheets) (Elias and Scherrick, 1969). Cytokeratin filaments show a symmetrical distribution in relation to the nuclear region. The highest density of filaments is found near the cytoplasmic membrane (Vassy et al. 1996). During development of fetal hepatocytes variations in cytokeratin networks can be correlated with different steps in cell differentiation. The special expression of intermediate filament proteins in fetal liver cells is reflective of the particular environment of the fetal liver in terms of extracellular matrix composition and intercellular contacts. Furthermore, the intracellular distribution of these CK proteins could be influenced by the cellular environment.

Immunohistochemistry can help to identify the various components of the intrahepatic biliary system in normal liver tissue. Markers such as polyclonal carcinoembryonic antigen and CD10 are also quite widely used in diagnostic practice to highlight bile canalicular differentiation in hepatocellular neoplasms and clearly identify the same structures within normal liver. CK7 and CK19 are strongly expressed by interlobular bile ducts, intraportal and intralobular bile ductules and the biliary epithelial cells that partly line the canals of Herring (Bateman and Hubscher 2010). It has been suggested that the individual CK7+ and CK19+ cells that partly line the canals of Herring represent hepatic progenitor cells. Biliary epithelial cells also express CK8 and CK18. In contrast, normal hepatocytes express CK8 and CK18 but not CK7 or CK19.

Thus, the liver forms a multicellular system, where parenchymal cells (i.e., hepatocytes) exert diverse metabolic functions and nonparenchymal epithelial cells (e.g., biliary epithelial cells) usually serve structural and other accessory purposes. In terms of differential CK gene expression, the data accumulated so far demonstrates that parenchymal cells can contain as few as one single CK pair, whereas nonparenchymal cells contain more than two CKs, one of them being a representative of those found in epidermis. Moreover, the distribution of the CK IF networks present in the different cell types varies a lot and can often be linked to the cell specialization. However, the function(s) played by these IF proteins in this multicellular tissue remains a major issue.

5. Role of cytokeratins in liver diseases

The concept of progenitor cells with the ability for maturation into biliary epithelium and hepatocytes is supported by *in vivo* studies of human liver disease. For example, CK7 immunohistochemistry in chronic viral hepatitis and autoimmune hepatitis highlights a bile ductular reaction and individual cells within hepatic lobules thought to represent progenitor cells. CK7 expression is also seen in hepatocytes in these conditions. This has been interpreted as *in vivo* evidence that progenitor cells can differentiate into ductular cells and mature hepatocytes in response to the chronic liver injury associated with these diseases, in contrast to the previously held view that mature hepatocytes at the limiting plate transform via metaplasia into biliary ductal cells. The degree of bile ductular reaction, progenitor cell numbers and proportion of hepatocytes expressing CK7 increases in parallel with disease grade (activity) and stage (Eleazar, Memeo et al. 2004; Fotiadu, Tzioufa et al. 2004). The positive association between hepatocyte CK7 expression and disease stage suggests that the increased extracellular matrix present in severe fibrosis and cirrhosis may produce a survival or maturation factor for progenitor cells (Eleazar, Memeo et al. 2004).

Mutations in the genes encoding CK proteins either directly cause or predispose their carriers to many human diseases (Coulombe and Omary 2002; Omary, Coulombe et al. 2004). The liver appears to be the primary target organ, with mutations in the genes KRT8, KRT18 and KRT19, which encode CK8, CK18 and CK19, respectively. Such mutations have been reported to predispose individuals to liver diseases (Ku, Wright et al. 1997; Ku, Gish et al. 2001). Furthermore, CK also have disease relevance in other contexts e.g they are important in the formation of hepatocyte Mallory-Denk bodies, which are hepatic inclusions observed in various chronic liver diseases (Zatloukal, French et al. 2007). Mallory-Denk bodies are found mainly in hepatocytes of patients with alcoholic and nonalcoholic steatohepatitis, but are also found in the hepatocytes of patients with primary biliary cirrhosis, hepatocellular carcinomas, and copper metabolism disorders (Zatloukal, French et al. 2007). Stress conditions may affect not only CK expression profiles, but also the levels of CK expression and posttranslational modification. For example, increased CK phophorylation is a marker of tissue injury and disease progression in human and mouse liver (Omary, Ku et al. 2009). Under certain stress conditions, increased CK expression may contribute to important cytoprotection provided by CK8 and CK18 in the liver. However, the importance of such upregulation has not been directly demonstrated (Ku, Strnad et al. 2007). These findings are supported by the observation of CK8 and CK18 over expression after injury in patients with primary biliary cirrhosis (Fickert, Trauner et al. 2003). In our own studies, we have found markedly increased levels of CK19 expression in patients with

autoimmune liver diseases such as primary sclerosing cholangitis, primary biliary cirrhosis and autoimmune hepatitis (Figure 2). We currently do not know the significance of increased CK19 expression in these diseases, but speculate that it may be a marker of liver tissue injury or disease progression in PSC and PBC patients.

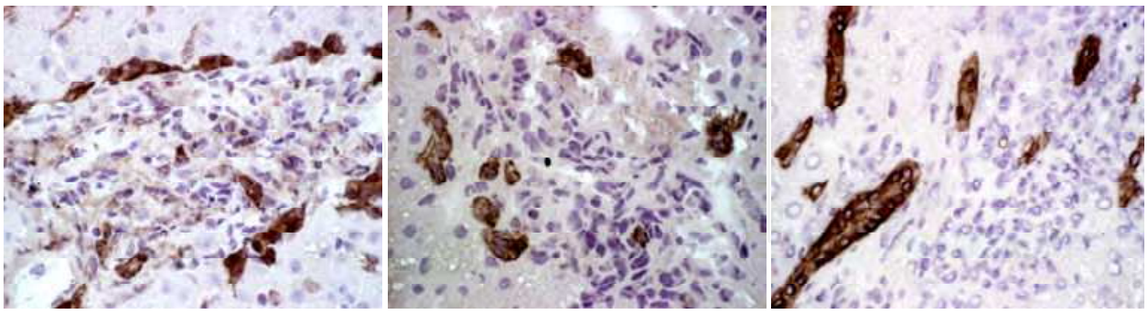

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Fig. 2. Immunohistochemical staining of liver biopsies from patients with (A) Primary sclerosing cholangitis, (B) Primary biliary cirrhosis and (C) Autoimmune hepatitis showing markedly increased expression of CK19 in the bile ducts of these patients.

6. Understanding CK-related liver diseases via transgenic animal models

Important information regarding keratin function *in vivo* has been obtained by the use of CK knockout and transgenic mice which has lead to the identification of human diseases that are related to mutations in genes encoding CK (Ku, Strnad et al. 2007). CK8-deficient C57BL/6 mice were the first mice to be generated. These mice exhibited liver hemorrhage and greater than 90% embryo lethality (Baribault, Price et al. 1993). When the surviving mice were further backcrossed onto an FVB background, it resulted in generation of mice with 50% embryo lethality. Although the surviving mice had a normal life span, they exhibited an ulcerative colitis–like phenotype (Baribault, Penner et al. 1994; Toivola, Krishnan et al. 2004; Habtezion, Toivola et al. 2005) and considerable hepatocyte fragility and susceptibility to liver injury (Loranger, Duclos et al. 1997). Although both CK8- and CK18-deficient mice lack hepatocyte keratin filaments, their phenotype is partially different. For example, no embryo lethality or colitis is observed in CK18-deficient mixed-background mice because of functional redundancy with CK19 (Magin, Schroder et al. 1998). However, both CK8-null and CK18-null mice have increased hepatocyte fragility (Loranger, Duclos et al. 1997; Ku and Omary 2006) and susceptibility to hepatocyte apoptosis (Oshima 2002; Marceau, Schutte et al. 2007). The first clear and detailed link between CK and liver disease came from mice that over expressed the R90C mutant of CK18. These mice exhibited mild chronic hepatitis and substantial hepatocyte fragility upon liver perfusion (Ku, Michie et al. 1995), with dramatic susceptibility to liver injury (Ku, Michie et al. 1996). It was this observation that led to the testing and initial identification of mutations in KRT18 and then KRT8 (Ku, Strnad et al. 2007) in patients with liver disease.

Transgenic mouse studies have also helped undersand how naturally occurring human mutations in the genes encoding CK predispose to liver disease. For example, over expression of the natural human G62C K8 mutant in transgenic mice leads to increased hepatocyte apoptosis and liver injury (Ku and Omary 2006). This predisposition is related to

a mutation-mediated conformational change that blocks CK8 S74 phosphorylation by stress kinases (Ku and Omary 2006; Tao, Nakamichi et al. 2006). The importance of CK phosphorylation in protecting cells from stress is further supported by the increased risk for liver injury in mice that over express the S53A K18 phosphomutant (Ku, Michie et al. 1998). Furthermore, transgenic mice that over express the S34A K18 mutant, cannot bind 14-3-3 proteins, leading to limited mitotic arrest (Ku, Michie et al. 2002). Altogether, these genetically engineered mice ultimately led to the association of keratin mutations with human liver disease and to understanding some of the involved pathogenic mechanisms.

7. CK as serum markers and CK variants in liver diseases

Mutations in the genes encoding keratins cause several human diseases, (Coulombe and Omary 2002; Omary, Coulombe et al. 2004). The association of CK variants with human acute and chronic liver disease is supported by numerous studies. For chronic liver disease, KRT8 and KRT18 variants are found to be overrepresented in patients with end stage liver disease of multiple etiologies (Zatloukal, French et al. 2007). Interestingly, PBC was the first human disease reported to be associated with CK19 and CK8 variants (Zhong, Strnad et al. 2009).

CK or CK fragments circulating in serum, which are released from apoptotic or necrotic tumor and non-tumor cells, have been used as tumor markers for monitoring disease progression in several cancers (Linder 2007). The most commonly used markers are tissue polypeptide antigen (TPA; a mixture of CK8, CK18, and CK19), tissue polypeptide–specific antigen (TPS; derived from CK18), cytokeratin fragment 21-1 (CYFRA 21-1; derived from CK19) (Leers, Kolgen et al. 1999; Marceau, Schutte et al. 2007). High TPS levels have been reported in several liver disorders (Gonzalez-Quintela, Mallo et al. 2006).

8. Autoantibodies specific for CK in human liver diseases

Autoantibodies specific for CK have been reported in autoimmune and malignant liver diseases. A sub fraction of autoimmune hepatitis (AIH) patients harbors high titers of antibodies specific for CK8, CK18, and CK19 that decrease after steroid treatment (Murota, Nishioka et al. 2001). Moreover, CK8- and CK18-specific antibodies have been detected in patients with de novo AIH after liver transplantation, whereas liver transplant recipients without de novo AIH were seronegative for these antibodies (Inui, Sogo et al. 2005). These antibodies may develop as a consequence of recurrent or chronic cell death, which leads to exposure of the immune system to cytoplasmic proteins that are not normally present in the circulation. Other CK-targeted autoantibodies include antibodies specific for CK8/CK18; these have been found in association with cryptogenic acute liver failure, which may suggest an autoimmune pathogenesis (Berna, Ma et al. 2007). Proteomic analysis has revealed an increased frequency of CK8-specific antibodies in patients with hepatocellular carcinoma compared with patients with chronic viral hepatitis. However, controversy exists regarding these results (Le Naour, Brichory et al. 2002; Li, Chen et al. 2008). Similar to the situation of CK serum markers, the presence of CK-specific autoantibodies may provide potentially useful clinical tools for diagnosis and determining prognosis and treatment response, but additional studies are required.

9. Intestinal cytokeratins – Model to study cytokeratin changes during differentiation and apoptosis

Main function of cytokeratins is to give mechanical support to the cell. But along with this static function they also play a role in dynamic processes like mitosis, cell movement and differentiation (Chandler, Calnek et al. 1991; Corden and McLean 1996; Ku, Zhou et al. 1999). Cytokeratin composition of the cell changes during these processes fulfilling the different needs of the cell during these processes, e.g. in non-dividing terminally differentiated cells, the role of the CK is to give a physical support to the cell which role is not so much important in rapidly dividing cells where rapid CK remodeling is essential. During proliferation phase it is important to respond rapidly to the cell signals by undergoing polymerization and depolymarization. As CK heterodimers differ in their viscoelastic properties and ability to undergo rapid polymerazation-demolymerization, CK pattern also changes in the same epithelial cell during division phase and maturation phase.

Intestinal epithelial cells provide an excellent model, for the study of these diverse functions, as these cells undergo proliferation, differentiation and apoptosis processes within a very short period of time. During their migration from crypt to villus region, cells undergo division cycles in the crypt region, differentiation phase along the villus and apoptosis at the tip of the villi. All these phases are thus temporally arranged along the crypt-villus axis. By studying CK pattern along crypt-villus axis, we can speculate how CK pattern changes during different phases of the cells.

In intestinal epithelial cells major type II cytokeratin present is CK8 (Moll, Franke et al. 1982; Zhou, Toivola et al. 2003; Omary, Ku et al. 2009; Habtezion, Toivola et al. 2011). Presence of CK7 is reported in some studies (Moll, Franke et al. 1982; Casanova, Bravo et al. 1995; Wildi, Kleeff et al. 1999; Zhou, Toivola et al. 2003; Schutte, Henfling et al. 2004; Toivola, Krishnan et al. 2004; Moll, Divo et al. 2008; Omary, Ku et al. 2009; Habtezion, Toivola et al. 2011) while there are also some reports stating the absence of this CK in the intestine (Ramaekers, Huysmans et al. 1987; Oriolo, Wald et al. 2007). Several type I cytokeratins are present in intestinal epithelial cells. Along with usual partner of CK8, i.e. CK18, these cells also contains CK19 and CK20. Presence of multiple type I cytokeratins is not redundant as gene replacement studies have shown that defect in any type I cytokeratin may lead to defect in the cells morphology and function. Additional cytokeratin filaments present in the intestine may be due to requirement of more structural strength by these cells as among the internal organs, intestine is subjected to more mechanical stress because of the movement of the luminal content (Owens, Wilson et al. 2004).

10. Expression along crypt-villus axis

The intestinal cells along the crypt-villus axis differ in structure as well as in function which in also reflected in different cytokeratins composition of these cells (Quaroni, Calnek et al. 1991). These changes along the crypt-villus axis are more apparent in animals than in human intestine. CK8, CK18 and C19 were found to be present along entire crypt-villus axis in humans while in rats CK18 is absent in villus cells. In rats, crypt cells also showed presence of CK7 (Omary, Ku et al. 2009). Human CK20 and its rat homologous CK21 is present exclusively in differentiated villus cells (Zhou, Toivola et al. 2003). Till today it has been found to be difficult to attribute a specific function to individual keratin so it is difficult

to predict the reason for these differences. One hypothesis is that cytokeratin filaments are observed to be associated with both desmosomes as well as microvillar rootlets. These components are present only in mature villus cells and not in immature crypt cells (Fath, Obenauf et al. 1990; Heintzelman and Mooseker 1990; Quaroni 1999). And also the extensive cytokeratin filaments are necessary to maintain the structural strength in mature villus cells, while it is deleterious for rapidly dividing crypt cells. CK20 expression in villus enterocyte may be related to the differentiated state of these cells and also the apoptosis process observed in the villus tip cells, as CK20 plays role in changes in cell shape required for exfoliation (Zhou, Cadrin et al. 2006). CK19 is preferentially localized in the apical domain of the several polarized cultured cells and down regulation of this cytokeratin using antisense nucleotides decreased the number of microvilli and also mis-sorted the targeting of apically distributed proteins. Distribution of basolateral proteins remains unaffected. But it is difficult to attribute these changes to the CK19, as changes in microtubules and microfilament was also observed in these cells. Thus, both crypt and villus cells different in the structure and function which can be observed in their different cytokeratin composition.

11. Cytokeratin changes during fetal development

Cytokeratin composition of the cells varies during embryonic development as well (Quaroni, Calnek et al. 1991). Changes in CK composition during fetal intestinal development were studied in rats. These changes are similar to the changes observed during differentiation in adult mucosa. In these animals stratified epithelium is present at the 15-16 days of gestation during which time CK19 is predominantly present with small amount of CK8. Expression of CK21 was observed when brush border and apical cytoplasmic terminal web formation starts at 18-19 days of gestation. In humans K20 appears at embryonic week 8 (Moll, Divo et al. 2008). There is also increase in the relative abundance of CK8 at this period. In adult human intestine expression of CK20 is observed along the villus cells while in fetal intestine some CK20 – negative cells were observed. Such mosaic distribution of CK20 – negative cells was not observed in fetal rat intestine (Moll, Zimbelmann et al. 1993).

12. Cytokeratin changes in animal and human intestine

A difference is observed in CK composition between rat and human intestinal epithelial cells. In rats, CK8 and CK19 are the major keratins, while CK18 and CK21 are less abundant. CK21 is homologous to human CK20 (Calnek and Quaroni 1993; Bragulla and Homberger 2009). This keratin is present only in differentiated villus cells in both rats and human. In rats, only type I keratin, CK19 is present in crypt cells while in humans CK18 and CK19 were found to be present in these cells. Uniform distribution of CK8, CK18 and CK19 has been observed along the crypt villus axis in humans while in rats, the common partner of CK8 i.e. CK18 was not observed in villus cells.

We studied the keratin expression in normal adult intestinal sample and also in cultured epithelial cells from these samples (n=5). Fig. 3 (a-d) shows cytokeratin filament network of human small intestine stained for CK8, CK18, CK19 and CK20 respectively. Entire epithelial layer showed positive staining for CK8, CK18 and CK19. But staining intensity for these CK is less in crypt cells compared to the intensity in villus cells. Bright CK positive staining is observed near the apical and basolateral membrane along with cytoplasmic staining for CK8, CK18 and CK19 but not for CK20.

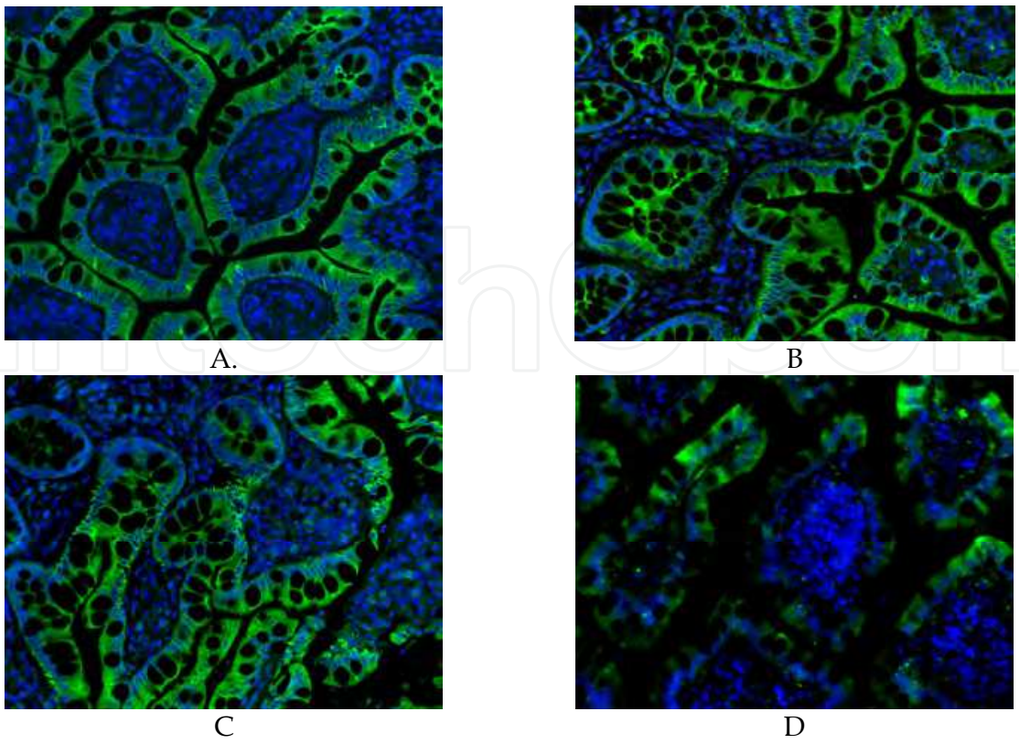

Fig. 3. Human small intestine stained for cytokeratins. Positive immunofluorescence staining for (A) CK8, (B) CK18, (C) CK19 and (D) CK20 was observed. These cells showed positive staining in the cytoplasm but intense staining is also observed along the membrane for CK8, CK18 and CK19.

13. Cytokeratin and related diseases

Cytokeratin mutation and intestinal disorders is the subject of many studies (Owens and Lane 2004; Owens, Wilson et al. 2004). As CK8 is the only Type II cytokeratin present in the intestine, mutation in CK8 affect the intestinal epithelium. Intestinal phenotype of CK8 null mice is similar to IBD phenotype. There are studies reporting the mutation in CK genes in subset of IBD patients (Owens, Wilson et al. 2004). A single amino acid change in CK8 leads to homo-dimer formation (Owens, Wilson et al. 2004) and CK are rapidly degraded when are not present as a heterodimer. This impaired CK assembly may make these cells more prone to the mechanical damage and creating a defect in the integrity of epithelial layer. And it is also observed that CK defect may affect the permeability of intestinal epithelial layer (Owens, Wilson et al. 2004; Toivola, Krishnan et al. 2004) which is one of the features observed in IBD patients. Apical membrane proteins of intestinal epithelial cells can affect the micro-flora present in the lumen (Hooper, Falk et al. 2000). Cytokeratin defects can alter the membrane proteins and hence the luminal flora which may result into the inflammatory reactions (Ameen, Figueroa et al. 2001). Thus type II cytokeratin mutation may contribute to a risk of IBD. Mutation in CK18 does not adversely affect the intestine probably because of the presence of other type I cytokeratins (Zhou, Toivola et al. 2003; Hesse, Grund et al. 2007). Even though cytokeratin related diseases are rare, many studies revealed that mutations in these proteins, predisposes the cell to diseases.

Tissue	CK7	CK8	CK18	CK19	CK20	Ref.
LIVER						
Developing hepatocytes	+	+	+	+	-	(Omary, Coulombe et al. 2004; Bateman and Hubscher 2010)
Developing bile ducts	(+)	+	+	+	-	(Bateman and Hubscher 2010)
Adult Hepatocytes	-	+	+	-	-	(Omary, Coulombe et al. 2004; Bateman and Hubscher 2010)
Adult bile ducts	+	-	-	+	-	(Bateman and Hubscher 2010)
Liver diseases						
Primary biliary cirrhosis	+	+	+	+	-	(Fickert, Trauner et al. 2003; Bateman and Hubscher 2010)
Autoimmune hepatitis	(+)	-	-	-	+	(Bateman and Hubscher 2010)
Primary Sclerosing Cholangitis	+	-	-	+	-	(Bateman and Hubscher 2010)
Alcoholic cirrhosis	+	-	-	(+)	-	(Vaneyken, Sciot et al. 1988; Ku, Strnad et al. 2007)
Hepatocellularcarcinoma	(-)	+	+	(?)	-	(Chu and Weiss 2002; Tot 2002; Moll, Divo et al. 2008)
Cholangiocarcinoma	+	+	+	-	-	(Chu and Weiss 2002; Tot 2002; Moll, Divo et al. 2008)
Intestine						
Rodent crypt cells	+	(+)	+	+	-	(Flint, Pemberton et al. 1994; Zhou, Toivola et al. 2003)
Rodent villus cells	-	+	-	+	+	(Quaroni, Calnek et al. 1991; Flint, Pemberton et al. 1994)
Human crypt cells	+ (?)	+	+	+	-	(Owens, Wilson et al. 2004; Toivola, Krishnan et al. 2004)
Human villus cells	+ (?)	+	+	+	+	(Owens, Wilson et al. 2004; Toivola, Krishnan et al. 2004)

Intestine diseases						
Colon cancer	+ (some cases)	+	+	+	+	(Harbaum, Pollheimer et al. 2011; Karantza 2011)
IBD	NR	-	NR	NR	NR	(Caulin, Ware et al. 2000; Owens and Lane 2004)
Colonic hyperplasia	NR	-	NR	NR	NR	(Baribault, Penner et al. 1994)

Table 1. Cytokeratin expression in Livers and intestine

14. Conclusion

The study of CK expression in the liver and intestine during development provides a useful insight into the mechanisms underlying stem cell activity and tissue remodeling in embryology. The previous concept that mature hepatocytes undergo metaplasia into bile ductular cells is now questioned and a new hypothesis that bipotential progenitor cells residing in the canals of herring may play a more important role in understanding the mechanisms of various liver diseases where cytokeratin expression has been found to aid in clinical diagnosis. Individuals with mutations in the genes encoding CK are more susceptible to various liver and intestinal diseases. However, further studies which include specific acute and chronic liver and intestinal disorders are required to fully assess the relative importance of CK mutations. Furthermore CK expression in intestinal epithelia is very complex and restricted to specific enterocyte subpopulations, yet the functional implications are not known. Further work in understanding the functions of CK7, CK19 and CK20 in the intestine is validated. Thus, the complex but interesting field of cytokeratins provides an important area for further investigation.

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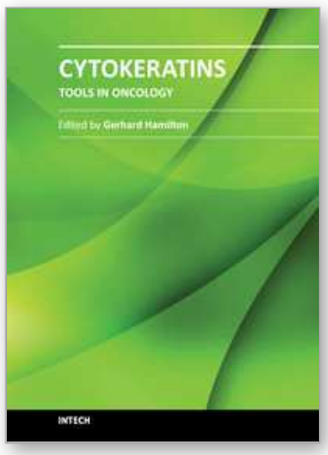

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The first chapters of the volume "Cytokeratins - Tools in Oncology" discuss multiple functions of cytokeratins in organization of the intermediary filaments in normal intestine and liver as well as microfold L cells and the usability of cytokeratins 7, 8 and 20 in tumor diagnosis in detail. Epithelial to mesenchymal transition as a mechanism important in pathogenesis is touched in another chapter, followed by several articles dealing with the role of cytokeratins for detection of disseminated tumor cells and as response markers during chemotherapy. This book is therefore destined to all cancer researchers and therapists who want to understand the diagnostic application of cytokeratins in histology and, especially, the use of anti-cytokeratin antibodies to identify viable residual tumor cells accounting for a higher risk of tumor recurrence or cancer cells responding to chemotherapy, respectively.

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