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EDITORIAL

Ontogeny, growth and development of the small intestine: Understanding pediatric gastroenterology

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Abstract

Throughout our lifetime, the intestine changes. Some alterations in its form and function may be genetically determined, and some are the result of adaptation to diet, temperature, or stress. The critical period programming of the intestine can be modified, such as from subtle differences in the types and ratios of n3:m6 fatty acids in the diet of the pregnant mother, or in the diet of the weanlings. This early forced adaptation may persist in later life, such as the unwanted increased intestinal absorption of sugars, fatty acids and cholesterol. Thus, the ontogeny, early growth and development of the intestine is important for the adult gastroenterologist to appreciate, because of the potential for these early life events to affect the responsiveness of the intestine to physiological or pathological challenges in later life.

Key words: Intestinal development; Ontogeny; Pediatrics

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INTRODUCTION

The molecular mechanisms of fetal development of the intestine have been explored using transgenic and knockout mice, with the suggestion of the importance of Wnt, bone morphogenetic protein (BMP), PTEN/PI3K and Notch signaling[1]. After midgestation, the stratified cuboidal intestinal epithelium, derived from endoderm, begins to form villi as a result of epithelial-mesenchymal interactions[2]. Wnt and Indian hedgehog signaling interact to stimulate proliferation and to act as a morphogen, in turn acting on BMP signals in the mesenchyme to influence morphogenesis during the development of the intestine[3]. The cellular differentiation along the crypt-villus axis is maintained by Wnt pathway target genes[4,5]. Unphosphorylated active PTEN in turn controls the activation of the lipid kinase PI3 kinase pathway, where the PDK1 and especially the PKB (Akt) ser1Thr kinases act as the main effecter kinases of this proliferative pathway[6].

These complex processes are integrated to produce functionally important alterations during late intrauterine and early postnatal life of intestinal morphology and function, to prepare the infant for early feeding on high-fat milk, and then weaning onto lower fat-but higher carbohydrate-containing solid foods. Understanding these ontogenic events helps to understand the early age-dependent approach to nutritional disease state.

INTESTINAL MORPHOLOGY

At the time of birth, the human small intestine is morphologically and biochemically more mature than that of other mammals. Of interest though, since rodents are born at a more immature stage than humans, at least some of the brush border membrane (BBM) enzymatic maturation that occurs prenatally in humans only occurs after birth in rodents. This makes the rodent a useful model to better understand the process of intestinal maturation that occurs in premature infants.

The maturity of the small intestine is reflective of the length of the gestational period, with the developments of the human small intestine being largely completed in utero by the end of the first trimester[7]. Despite temporal differences in the ontogeny of the small intestine between species, the processes involved in the development of the small intestine remain similar. Thus, the human intestine goes through each of the stages that occur in rodents, so that animal studies may be used to better understand the development of the human intestine.

Development of the small intestine is comprised of three stages: (1) morphogenesis and cell proliferation, (2) cell differentiation, and (3) functional maturation[8]. Gastrulation is the process by which the primitive gut tube is formed. This consists of the endoderm, the precursor to the epithelial lining of the gastrointestinal (GI) tract, surrounded by mesenchyme. In humans, this process begins at three weeks gestation[7].

In the embryo, the GI system is one of the first to polarize by forming an entry and exit to the systems along the anterior and posterior axis. The *hox* genes are nuclear transcription factors that activate genes that encode secretory proteins. The *hox* genes play an important role in the formation of distinct regions of the brain and skeleton[7]. Through epithelial-mesenchyme interactions, these proteins may also be involved in determining anterior-posterior patterning in the fetal gut. Similarly, Sonic hedgehog and Indian hedgehog pathways mediate epithelial-mesenchymal interactions at early stages of gut formation[2].

Next, there is a transition into columnar epithelium, with the development of polarized enterocytes, and the formation of the BBM and basolateral membrane (BLM) of the enterocyte. The formation of nascent villi and microvilli occurs simultaneously, with cellular proliferation detectable along the villi. In humans, formation of the villus is initiated at 9-10 wk gestation, and proceeds in a cranial-caudal direction[7]. Villus and microvillus formation account for the approximate 100 000-fold increase in the intestinal surface area observed from the early first trimester period to birth[9].

The development of intestinal crypts then follows in humans, but in rodents, crypts do not develop until after birth[10]. The human fetus and the neonatal rat have transient villus-like structures in the proximal colon with properties similar to enterocytes, including the expression of BBM enzymes and transporters[11-13]. In later life, when premalignant changes occur in the colon in the form of development of colonic adenomatous polyps, the villous structure may recur. Interestingly, $CaCO_2$ cells derived from human colon cancer cells develop villi and villous functions, and are a good cell culture model for the assessment of, for example, intestinal absorption and metabolism.

The cells of the intestinal mucosa (the antagonists, enteroendocrine cells, Paneth and goblet cells) are compartmentalized within the crypt-villus unit. All four of the differentiated cell types of the intestinal mucosa are derived from one or more multipotent stem cells located in each intestinal crypt[14]. As cells move out of the crypt and up the villus or deeper into the crypts, "…differentiation occurs as progeny of the transit cell population migrate in vertically coherent bands…"[15]. Fibroblast growth factor receptor 3 (FGFR-3) is highly expressed in the undifferentiated crypt epithelial cells in the developing intestine, and FGFR-3 signaling through β-catenin/Tcf-4-dependent and independent pathways may regulate crypt epithelial stem cell expansion and crypt morphogenesis by the process of crypt bifurcation or fission[15]. Other growth factors such as Wnt(s) and FGF2 may cross talk with the β-catenin signaling pathway[16].

Cellular proliferation occurs in the crypts, differentiated cells populate the villi, and the dynamic balance between proliferation and differentiation is balanced by apoptosis of the senescent cells. Hepatocyte nuclear factor 4 α (HNF4α) belongs to the family of nuclear receptor transcription factors found in the liver, pancreas, kidney, and intestinal tract[17,18]. HNF4α may instruct "… cells to become specific to the intestinal epithelium"[19], as well as upregulating genes during epithelial cell differentiation such as Apo A-Ⅳ, intestinal alkaline phosphatase, liver and intestinal fatty acid binding proteins[20-23].

Bile acids regulate their own synthesis[24]. The luminal concentration of bile acids and the bile acid pool are low in the preterm and term infant, and rise as the animal ages[25,26]. These initially low values are associated with malabsorption of lipids[27]. The size of the bile acid pool increases with the activity of cholesterol 7α-hydroxylase (Cyp7a1) and oxysterol 7α-hydroxylase (Cyp7b1) by mechanisms that are independent of the farnesyl X receptor (FXR), and the short heterodimeric pathway (SHP)[24].

Increased bile acid absorption by the ileal apical sodium-dependent bile acid cotransporter (ASBT) also contributes to the expansion of the bile acid pool.

In mouse models of necrotizing enterocolitis (NEC)[28], the preinflammatory transcription factor NF-κβ mediates this intestinal injury as the result of platelet activating factor (PAF) converting p105 into p50. The p50 further upregulates proinflammatory cytokines which lead to a systemic inflammatory response and acute bowel injury[29].

Peroxisome proliferator-activated receptor-j (PPARj) is a nuclear receptor which associates with retinoid X receptor to "…suppress proliferation and promote differentiation of intestinal epithelial cells…", and to decrease the size of the proliferative zone of the intestinal crypts[30-32]. The thiazolidinedione drugs are PPARj ago-

nists which reduce cholera lexin mediated chloride secretion through the reduced expression of the apical CFTR channels, KCNQ1 K^+ channels as well as Na^+-K^+-$2Cl^-$ cotransporter-1 proteins in the BLM[33].

In addition to the enterocytes, four other small intestinal mucosal cell types develop: goblet cells, enteroendocrine cells, Paneth cells, and M cells. M cells are associated with Peyer's patches, and are detected by 17 wk of gestation[34]. In the human intestine, all epithelial cell types known to occur in the adult are present by the end of the first trimester[34]. The intestinal epithelium is able to maintain the differentiation programs of each lineage, depending on the location of the cells along the crypt-villous and proximal-distal gradients[35,36].

The regulation of GI development is complex, and involves a host of growth and transcription factors. Receptors for epidermal growth factor (EGF), transforming growth factor β (TGFβ), insulin-like growth factor Ⅱ (IGF-Ⅱ), hepatocyte growth factor (HGF), and GLP-2 are present in fetal human intestine[37,38]. Human fetal cortisone levels in the blood increase late in gestation[39]. Corticosterone (a glucocorticoid similar to cortisol) is thought to be the main factor involved in rat small intestinal maturation[40,41].

Studies investigating the development of human fetal small intestine xenografted to SCID mice demonstrate that the transplanted intestine normally undergoes differentiation in the absence of luminal and hormonal factors[42,43]. This finding, in conjunction with the observation that villus formation in rodents is autonomous[44], suggests that intestinal development may be "hard-wired", i.e. is regulated largely by intrinsic factors, with extrinsic factors playing only a secondary role. Indeed, several transcription factors including *N-myc*, HNF3β and C*dx-2* have been identified as potential intrinsic factors implicated in GI development. *N-myc* gene knockout animals demonstrate defects in GI development[45]. Homologous null mutants of HNF3β are lethal, as many structures, including the gut tube do not develop normally[46,47]. Cdx-2 expression is detected at the time of morphogenesis in mouse intestine, and is a known regulator of the expression of the small intestinal BBM enzymes sucrase-isomaltase (SI)[48].

The exogenous expression of Cdx-2 in a rat intestinal cell line induces the differentiation of goblet and absorptive cells from crypt cells. This suggests a possible role of Cdx-2 in the ontogeny of the GI tract. Several other signaling pathways (including the Notch, Wnt/β-catenin and BMP pathways) are also thought to play a role in patterning the gut during development, and in regulating epithelial differentiation through epithelial-mesenchymal interactions[49,50]. What then is the importance of the extracellular matrix (ECM)?

Indeed, in addition to regulation by transcriptional factors, intestinal development may be controlled through interactions with components of the ECM. Developmental changes in E-cadherins and integrins have been described[36,51,52], suggesting that the ECM may influence the ontogeny of epithelial cells. Cultures of human fetal enterocytes demonstrate enhanced differentiation, when they are grown on components of the ECM[53]. This suggests that a permissive rather than an instructive role may be attributed to the ECM in GI development. Indeed, when major components of the ECM have been deleted, in mice, they show no changes in GI morphogenesis, indicating that these components are not essential for GI development in this model[54].

FUNCTIONAL DEVELOPMENT

The functional development of the BBM enzyme activity has been well characterized[55-58].

BBM SI is first detected in the human fetus in the first trimester, but is not seen until weaning in the rat[58]. Both rat and human fetal small intestine demonstrate detectable BBM lactase-phlorizin hydrolase (LPH) activity, but LPH expression before and after birth varies depending on the species[59]. In humans, BBM enzyme activity has been correlated to morphogenesis, with the development of enzyme activity being associated with the formation of enterocytes[60]. Proximal-to-distal gradients of enzyme activity along the length of the small intestine are established early in gestation. In addition, crypt-villous gradients are evident, with LPH activity being highest at the villous tip, and SI activity maximal in the mid-villous region[61].

LPH

The earliest ingested nutrient in mammals is, of course, milk. The major carbohydrate in milk is disaccharide lactose. Lactose is cleaved by BBM LPH into glucose and galactose. LPH is therefore a crucial enzyme for neonates who are solely dependent on their mother's milk for nourishment.

Human LPH is first detected in the proximal small intestine at 8-9 wk of gestation, but later extends along the length of the small intestine[60]. In contrast, rat LPH is very low until 24 wk gestation, when its activity begins to increase. A rise in LPH activity in rodents occurs only late in the third trimester. In the human fetal jejunum, LPH activity correlated with the abundance of its mRNA[62], consistent with the proposal that LPH activity is regulated transcriptionally[63-65]. Nuclear transcription factors that have been shown to interact with the LPH promoter element CE-LPH1 include CDX-2[66], HOXC11[67]), GATA6[68], and HNF1[67].

Once weaning has occurred in nearly all species of mammals, both LPH activity and mRNA abundance decline[59,69,70]. Even in humans, the vast majority of the world's population experiences a decline in LPH activity sometime during childhood or adolescence. These lower values of LPH activity are 5%-10% of those values seen in early childhood[71]. In contrast, in geographical regions such as Western Europe and North America, where for thousands of years dairy cattle were raised as a continuing source of milk, LPH activity persists throughout adulthood[59,69,70], unless an adverse process affects the small

intestine. This is known as secondary lactose deficiency (i.e. the decline in LPH activity is secondary to a disease). The decline in LPH activity in early life in characteristic locations is primary, i.e. genetically determined. Thus, if an adult with northern European ancestry presents with new onset milk intolerance, lactose deficiency is suspected, and an underlying condition such as celiac disease or inflammatory bowel disease is looked for.

In humans, the correlation between mRNA abundance and activity of LPH suggest that transcriptional and post-transcriptional mechanisms are involved in the development of hypolactasia[72]. Post-translational mechanisms may also be involved in the decline in LPH activity, through the modulation of functional protein along the villus. Glycosylation of the protein results in the 225 kDa form, however, the mature BBM LPH enzyme represents a cleavage product of this glycosylated precursor[59,73,74]. The initial cleavage occurs intracellularly in a post-Golgi compartment[75]. This yields a protein which lacks LPH activity. Once LPH is inserted in enterocyte BBM, LPH is once again cleaved, but this time by extracellular trypsin, and this yields the mature and active 145 kDa form of the LPH and it is cleaved[76].

SI

SI is a bifunctional enterocyte BBM disaccharidase with sucrase, isomaltase and maltase activity. Sucrase hydrolyzes sucrose into glucose and fructose. In humans, SI is first detected at 9-10 wk gestation, and gradually increases until just prior to birth, when a marked increase in SI occurs. After birth, there is a rapid decline in SI levels to values comparable to those found in early gestation. Sucrase is not normally a part of the infant's diet, so it is not clear why SI activity is so high in the human fetus.

Fetal human SI protein is in the proSI form from 15-30 wk gestation, but after 30 wk most of the protein consists of sucrase and isomaltase subunits[77]. Enterokinase activity, which activates proteases that cleave proSI, appears at 26 wk, and coincides with the appearance of the sucrase and isomaltase subunits.

SI is transiently expressed in the colon of both humans and rodents[11,13,60,78] in association with the appearance of small intestinal-like morphology. The observation that SI is expressed in colorectal cancer cells suggests that the factors that normally repress SI expression in the colon may be lost in cancer cells.

In mice, low levels of SI mRNA abundance are detectable in the small intestine[78]. However, rat studies show that there is no BBM SI activity from birth until weaning[58]. Thus, even between different types of rodents there are variations in BBM SI development. At weaning, a dramatic increase in SI activity occurs, with adult rat levels being rapidly established. Expression of SI mRNA and protein is first detected in cells located at the crypt-villous junction, suggesting that the enterocytes containing SI are programmed in crypts. As these enterocytes migrate up the villus, the entire villus ultimately becomes populated with cells expressing SI. SI expression first appears in the proximal small intestine, and then proceeds distally to the ileum. This is a genetically programmed event that is not significantly affected by the animals' diet[70,79]. Premature SI induction can be induced by precocious stress, glucocorticosteroids, insulin, or thyroxine[70,79,80].

There is a correlaton between fetal SI activity and mRNA abundance, suggesting control at the level of either mRNA transcription or stability[81]. A number of regulatory elements (including SIF1, SIF2, and SIF3) have been identified within the promoter region of the *SI* gene, and are important for transcriptional induction. CDX-2 binds to the SIF1 element and transactivates the *SI* gene promoter[48]. CSX-2 appears to be the major regulator of SI transcription. A number of other potential transcription factors have been identified, such as HOXC11, which like CDX-2, bind to the SIF1 element of the SI promoter[67]. HNF1α interacts with the SIF3 element and to a lesser extent SIF2, to activate SI transcription[82]. GATA zinc-finger transcription factors interact with a region of the SI promoter upstream of the SIF1 element.

Glycosylation of the SI protein occurs in the endoplasmic reticulum (ER) and in the Golgi apparatus, yielding a 245 kDa protein[83]. Once the protein is inserted into the BBM, the post-translational processing is by the cleavage of the molecule into two subunits which occurs *via* trypsin digestion in the intestinal lumen[83]. The SI subunits remain associated by hydrostatic bonds. Defects in post-translational processing are thought to be responsible for inherited SI deficiency in humans[84].

Glucose transport

The ontogeny of intestinal nutrient transport is largely dependent on the species that is studied. In all mammals, sugar transporter protein does not appear until the intestine differentiates and forms crypts, villi and microvilli. The time at which this process occurs differs between species (please see above), and may be affected by the length of the gestational period. Differentiation of the mucosa alone, however, is not solely responsible for triggering the appearance of transporters, as many of them do not appear until after birth, or even after weaning.

Much of the research on the ontogeny of intestinal transport comes from rodent studies. Rodents are considered to be altricial, meaning that they are born "premature" as compared to humans. Indeed, many of the postnatal changes in the intestine seen in rats occurs parentally in humans, making neonatal rodents an ideal model for premature infants[85]. The pig is also a useful model of ontogeny, due to the similarities between the pig and the human small intestine[86].

The intestinal transport of nutrients, such as glucose, is first detected in the fetal small intestine of mammals, including humans[87]. Both placental nutrients[88,89] as well as the swallowing of amniotic fluid[90] contribute to fetal nutrient acquisition. In fact, the volumes of amniotic fluid which are swallowed in humans *in utero* at term are estimated to be approximately 500 mL/d[91]. Taste buds are detected early in gestation[92], and early experiments have shown that human fetal swallowing increases transamniotic saccharin infusion, and decreases following the

infusion of noxious substance[93]. Injection of galactose into the amniotic fluid of fetal rabbits increases intestinal mucosal weights, as well as the uptake of glucose[94]. Thus, even fetal rabbits are able to up-regulate intestinal transport capacity in response to nutrients. The importance of fetal swallowing in the development of the GI tact is also highlighted by experiments in which fetal sheep underwent esophageal ligation to prevent amniotic fluid from reaching the small intestine[95]. A decrease in small intestinal villous height, intestinal weight and body weight resulted.

Prenatal intestinal transporters are critical for the development of the fetus, as an estimated 10%-15% of fetal protein requirements in rhesus monkeys are met through nutrients that are present in the amniotic fluid[96]. The presence of growth factors released from the GI tract may also be important, as gastric infusion of epidermal growth factor (EGF) reversed the weight loss seen following esophageal ligation[90].

Once the epithelium lining the small intestine differentiates into columnar cells at 9-10 wk of gestation, transport BBM proteins including SGLT1 are expressed[97]. Significant levels of SGLT1 mRNA are also detected in fetal tissue, suggesting that carrier-mediated transport of glucose may be occurring[98]. Dramatic increases in the site density of SGLT1 are observed in fetal pigs between 74% of term and birth[98]. Between 17 and 30 wk gestation in humans, the duodenal-ileal gradient of glucose absorption is established[99]. In rats, glucose transport and SGLT1 protein and mRNA increase at weaning to levels higher than those seen in suckling or in adult animals[100,101]. Curiously, phloridzin does not block glucose transport by SGLT1 in suckling and mature animals to the same extent that it does in weanlings. This may suggest the presence of an age-specific alternative mechanism of glucose transport, or an age-related difference in the phloridzin binding site on SGLT1.

Kinetic analysis of glucose uptake rates in BBM vesicles from human fetal tissue suggests the presence of two transport systems. In addition to SGLT1, a low affinity, high capacity system is detected in the proximal small intestine[102,103]. This may represent GLUT2, which has been described in the BBM of adult rats exposed to high luminal sugar concentrations[104].

Human and rat fetal small intestine also express GLUT1 (as do erythrocytes and brain tissue), which appears earlier than GLUT2, and decreases gradually during fetal life[105,106]. Although the mechanism of this developmental regulation is unknown, GLUT1 may be involved in early cell growth proliferation. Intestinal BLM GLUT2 mRNA is expressed at high levels at birth[101], and GLUT2 transports glucose and fructose. In fact, GLUT2 mRNA is detected in fetal rats as early as day 16 following conception, even before intestinal villi are formed[106]. GLUT2 mRNA increases after weaning, and subsequently decreases to adult levels[101]. GLUT2 in the developing intestine is regulated by luminal glucose and fructose[107]. Luminal perfusion of 20 d old rat pups' intestine with fructose or glucose (100 mmol/L) increases GLUT2 mRNA. This enhancing effect of luminal glucose or fructose was blocked by the transcription inhibitor actinomycin D, but was not affected by the protein synthesis inhibitor cycloheximide. GLUT2 mRNA was also increased in bypassed intestinal loops, suggesting that systemic factors are involved in its regulation. Interestingly, GLUT2 mRNA abundance was even higher in the bypassed loop than in the section that was perfused, suggesting a possible compensatory mechanism due to perceived starvation.

Sugar uptake increases with the gestational age of the animal, and typically peaks immediately after birth, when the intestine takes over the burden of nutrient acquisition from the placenta. Studies done on pigs using the everted sleeve method demonstrate that the maximal transport rate (Vmax) for D-glucose was highest immediately after birth, with a subsequent decrease in the value of Vmax associated with the onset of suckling[86]. In contrast, in newborn pigs the onset of suckling appears to stimulate increases in BLM GLUT2 density[108]. It is not known if GLUT2 activity protein or mRNA can be modified by sugars in the intestinal tract of humans.

At birth, all enterocytes appear to have the capability to transport nutrients. As a result, uptake occurs in enterocytes from all along the villus, rather than just from the upper third, such as occurs in older rats[109]. This may contribute to the higher rate of sugar uptake. Soon after birth, the gradient of increasing transport as one moves from the crypt to the villus is established[109]. This may be responsible for the reduced uptake capacity of the intestine observed postnatally. The "dilution" of fetal enterocytes with new immature cells that do not express transporters may be responsible for this effect. Indeed, the subsequent age-related decline in transport observed in chickens was attributed to reductions in the site density of SGLT1[110].

Developmental changes in the intestinal transport of nutrients may also be non-specific (for example, changes in mucosal surface area, proliferation and migration of enterocytes, or changes in intestinal permeability). Indeed, the subsequent age-related decline in transport observed in chickens was attributed to reductions in the site density of SGLT1[110].

Studies on human premature neonates have used the urinary excretion of D-xylose and 3-O-methyl-glucose as measures as passive and active carrier-mediated monosaccharide absorption of these sugars, respectively, when compared to those born before 28 wk gestation[111]. The replacement of rat fetal enterocytes along the villus requires up to 2 wk, as compared to the 24-48 h required for the replacement of adult enterocytes. Non-specific changes are responsible for ontogenic alterations in mucosal weight, surface area and transport capacity. Postnatal development of enterocytes results in increases in the surface area of microvilli and the BLM[112,113]. Reduced turnover rates result in longer lifetimes of enterocytes, resulting in slower replacement of cells.

Reductions in BBM fluidity occur in post-weaning rabbits, in association with increases in the cholesterol-

to-phospholipid ratio in the BBM[114,115]. In general, reductions in fluidity result in reductions in permeability. Human neonates show decreases in intestinal permeability within the first 30 d of life, as assessed by lactulose/mannitol urinary excretion[116].

Fructose transport

Although SGLT1 and GLUT2 are expressed in enterocytes both in the fetus and at birth, the expression of BBM GLUT5 is only detected in post-weaning rats[101,117-119]. This contrasts with what is seen in pigs[86] and lambs[120]. In rats, GLUT5 protein and mRNA abundance parallel fructose transport, and therefore remain low throughout the suckling phase. GLUT5 protein and mRNA also remain low throughout weaning in rats, with higher levels detected in the post-weaning phase when fructose may first appear in the rat[101,118,119]. This increase in GLUT5 mRNA and protein coincides with the rise in fructose uptake seen at this period. Although there is a temporal association between the introduction of dietary fructose and the appearance of GLUT5, the expression of the transporter is "hard wired" and occurs at this time even in the absence of dietary stimuli[121]. However, the precocious introduction of fructose into the diet of 22 d old rat pups stimulates fructose transport and GLUT5 mRNA expression[121]. Jiang *et al*[122] showed that luminal perfusions of high concentrations (100 mmol/L) of fructose resulted in increases in GLUT5 mRNA and activity. This developmental reprogramming of fructose transport required *de novo* mRNA and protein synthesis, as both actinomycin D and cycloheximide (inhibitors of transcription and translation, respectively) abolished the effect.

In humans, the introduction of solid foods and fruit juice containing fructose at earlier stages of infancy, coupled with the increased use of fructose as a sweetener in dietary products, has resulted in increased exposure to fructose during infancy. Fructose has been implicated as the major cause of "toddler's diarrhea", largely because it is a late onset transporter that increases postnatally in human infants[123]. The infant intestine may not be equipped to absorb high amounts of fructose, resulting in fructose malabsorption. Fructose may then enter the colon, and the high osmolarity may cause osmotic diarrhea. Even in adults, the incidence of fructose intolerance may be increasing: in a recent study malabsorption may be over 70% in persons with persistent, unexplained, non-specific GI symptoms[124]. The dose of fructose used in this study was approximately equivalent to the amount of fructose found in two cans of pop.

Amino acid transport

Amino acid (AA) transporters appear prenatally in the intestines of chickens, rats, rabbits, and humans, and these transporters increase dramatically in the first days after birth[125]. In rats, rabbits, and pigs, the highest rates of BBM AA and peptide uptake are seen at birth, with decreases during suckling and post-weaning[126-128]. In rats, BBM AA transporters are expressed prenatally at the same time or shortly after SGLT1[129]. In 17-20 wk gestation human fetal small intestine, all of the AA transport systems studied (neutral, acidic, basic, and imino) were found to be functional, with a proximal-distal gradient established shortly after cypt-villus formation[130]. In human fetuses, AA transport occurs at 14 wk gestation, with glucose transport at 18 wk, and fatty acid absorption at 24 wk gestation[131].

AA transporters, including NBAT (which transports cationic and neutral AA) and EAAC1 (which transports glutamate), are expressed in suckling rats[132]. The intestinal absorption of peptides occurs *via* PepT1, which is distributed throughout the small intestine. The distribution of these transporters in suckling rats parallels that seen in adult animals. NBAT mRNA is highest in the proximal small intestine, while EAAC1 mRNA was highest in the more distal regions. While a marked crypt-villous gradient was found for PEPT1 and NBAT, EAAC1 immunoreactivity is confined to the lower third of the villus and to the crypts. Thus, the EAAC1 transporter of glutamate is the first AA transporter with decreased expression during epithelial cell differentiation[132].

There are developmental changes in AA and peptide transport. The ontogeny of AA transport is complicated due to the major species differences, and by the large number of AA transport systems, and the fact that some AA are essential or non-essential, depending on the age of the animal. Also protein requirements change throughout the lifespan of an animal, necessitating variations in either intake or uptake of protein or AA. For example, intestinal proline uptake per mg of tissue is maximal at birth in rats, decreases at the end of the suckling phase, and decreases further in older animals. This decline matches both the dietary protein levels and protein requirements[119]. In addition, the decline in uptake of essential AA is greater than that for non-essential AA[129]. This may be because young animals have a disproportionate need for essential AA in early life, due to their rapid growth at this age.

There are also different patterns of uptake for individual AA. For example, in cats, the basic AA transport declines more steeply than does neutral AA transport. In humans, lysine and phenylalanine transport appears later than does the transport of alanine, leucine, taurine and valine[133]. In rats, uptake declines at a similar rate with age from proline, methionine and lysine; however the decline in leucine uptake occurs twice as quickly[129]. Finally, in rats as transition occurs at weaning when the uptake of glucose, fructose, and lysine increase, this is coupled with decreases in proline and leucine uptake[119]. It is unknown why there are such complicated patterns of changes in AA uptake in early life.

Macromolecule transport

The uptake of macromolecules across the intestinal epithelial barrier is an important route by which immunoglobulins, growth factors and antigens are absorbed. This route of entry is especially important in neonates, who rely on it to obtain important immune factors from

maternal colostrum or milk. Most species (including rats, mice, and humans) are born hypoglobulinemic, and absorb IgG from maternal milk through proximal small intestine absorption[134,135].

The transport of macromolecules across the BBM may occur by receptor-mediated or non-specific transcytosis. The transport of macromolecules is facilitated by the presence of protease inhibitors in the maternal colostrum. Rodent studies demonstrate specific intestinal receptors that bind to the Fc portion of IgG[136]. These receptors are transcriptionally regulated, and are present in highest amounts in the duodenum[137]. In humans, IgG is transferred from the placenta to the fetus in the third trimester of pregnancy, with receptors for IgG being detected in the intestine of both the fetus and the neonate. Macromolecular movement across the BBM persists after birth, and then gradually decreases[136]. The initially high permeability of the intestine declines after birth, leading to a process commonly referred to as "gut closure". The time at which gut closure occurs and macromolecular transport ceases varies between species, with a rapid decrease in transport observed in pigs within the first few postnatal days, and a similar decrease seen around 21 d after birth in rats and rabbits[138]. In humans, the exact time that gut closure occurs is unknown, but intrinsic features as well as growth factors, hormones and breast milk may play a role in regulating this process. The decline in permeability may also be related to changes in the thickness and viscosity of the mucus gel layer which coats the BBM. The intervillus mucus gel is increased in weaned as compared to suckling rats. This would potentially increase the effective resistance of the unstirred water layer, and thereby contribute to the decrease in the uptake of macromolecules.

In human infants, uptake of macromolecules or lactoalbumin declines with advancing postconceptual and postnatal age[139]. The ability of the neonatal intestine to adapt to the presence or absence of luminal stimuli is apparent from studies demonstrating a delay in spontaneous closure of the intestine if breastfeeding is postponed beyond the first 30 h of life[140].

Pancreatic enzymes

The higher fecal fat losses in preterm infants compared with term infants is thought to be attributable to lower pancreatic and intestinal lipase activities. Despite the presence of lipase in breast milk and of lipases in the newborn tongue and stomach, micellar absorption of lipids appears later when pancreatic lipase and bile acid concentrations increase[141].

The human exocrine pancreas is functionally immature at birth, with substantial development occurring after birth. Proteolytic enzymes are detected early in the human fetus (20-25 wk gestation), with each enzyme developing in a unique manner. Trypsin increases during fetal life, to reach 90% of childhood levels at term[142]. In contrast, at birth chymotrypsin and carboxypeptidase B levels are less than 60% and 25% of childhood levels, respectively. Despite the differences in the temporal development of proteolytic enzymes, protein digestion in the preterm neonate is adequate, and may be supported by the early development of gastric pepsin and mucosal peptidases[143].

Pancreatic amylase activity is negligible in the human fetus, and is not detectable until one month after birth[144]. Salivary amylase is detected at 20 wk gestation, and while levels are low at birth, they increase to adult levels by the third month following birth[145]. Amylase is also present in human milk, and may aid in the digestion of starch contained in weaning foods[145]. The reduced levels of amylase activity may reflect the low levels of starch in the neonatal diet. At weaning, an increase in amylase activity is detected[144]. While this may be influenced by the appearance of starch in the infant's diet, animal studies demonstrate a persistent increase in amylase activity in rats subjected to prolonged nursing[146]. This suggests the presence of an inherent genetic program for the expression of amylase activity, not necessarily related to the starch content of the diet.

Pancreatic lipase activity in humans is detectable at 32 wk gestation. It remains low at birth, and increases 10 wk after birth[147]. Lingual and gastric lipases, however, are detected at 26 wk gestation[148]. At birth these lipases are able to hydrolyze 60%-70% of ingested fat, even in the absence of pancreatic lipase[149]. Lipase and esterase activity is present in human milk, and contributes to the increased fat absorption observed in breastfed infants[150]. Low lipolytic activity may be the rate-limiting step in the development of efficient fat absorption[143,151,152]. Authors propose that it is the ability to take up long chain fatty acids (LCFA) from the lumen that is the rate-limiting step[153].

The ontogeny of the intestine is "hard wired", and occurs even in the absence of luminal and hormonal factors[41,42]. Still, a number of studies have demonstrated that variations in maternal diets, as well as weaning diets, can influence the ontogeny of the intestine[154-156]. "Critical period programming" is a phenomenon by which a biological mechanism is irreversibly turned on or off once during a lifetime in response to prevailing conditions at a critical stage[157]. This concept, which has also been referred to as "metabolic programming" or "imprinting"[158,159], has been used to explain associations between prenatal/neonatal environment events, alterations in growth and development, and later pathophysiology[160,161]. Early exposure to a diet high in fructose during the suckling-weaning transition may contribute to modest dyslipidemia later in life[162]. Intestinal sugar uptake is also prone to critical period programming[163].

The role of dietary lipids in the programming of intestinal nutrient transport has been studied[154-156,164,165]. Thomson *et al*[164] demonstrated that feeding eight-week old rabbits a low cholesterol diet for two weeks reduced intestinal glucose uptake, and that this effect persisted for at least ten weeks after the animals returned to eating a normal diet. The response to diet depended on the duration of feeding, the age of the animals, and whether or not there was previous exposure to the diet. In this

study, effects on sugar transport were not explained by changes in food intake, body weight or intestinal weight. Furthermore, persistent changes were seen in the active transport of glucose, galactose, leucine and bile acids, while changes in the passive uptake of lipids were reversible.

When the ratio of polyunsaturated to saturated fatty acids in the diet of weanling rats is altered, diets enriched in saturated fatty acids increase hexose uptake, and these alterations were fast, progressive and irreversible[154]. Feeding the same diets to pregnant and lactating rats resulted in similar increases in sugar uptake in their weanling offspring[166]. Curiously, these changes were not seen in the suckling offspring, suggesting that the mechanisms responsible for adaptation may not be fully developed in these animals. Perin *et al*[165] confirmed that the weanling intestine was capable of adaptation, by continuing to feed the offspring of pregnant dams the same diet for three weeks post-weaning. Persistent alterations in sugar uptake were seen in response to variations in dietary lipids, once again emphasizing the importance of early exposure in the programming of intestinal nutrient transport. In addition to the differences between suckling and weanling offspring, the pattern of adaptation also appeared to differ between the jejunum and ileum.

Further studies went on to characterize the effect of diets enriched with arachidonic acid, docohexanoic acid and diets with different ratios of n6 to n3 fatty acids on intestinal nutrient transport[156]. As in the previous study by Perin *et al*[166], these maternal diets critically influenced the ontogeny of the intestine, with many of the changes in transport being irreversible. Furthermore, responsiveness to later dietary challenges depended on early-life feeding experiences, once again emphasizing the importance of early dietary exposure to the development and later adaptability of intestinal transport of nutrients.

Lipid and bile acid transport

Studies using human fetal jejunal explants (14-20 wk gestation) maintained in serum-free organ culture demonstrated increases in chylomicron, VLDL and HDL, paralleled by increases in triglycerides and cholesterol eaters. This demonstrates the ability of the fetal intestine to absorb fat in conjunction with ontogenic increases in lipid and lipoprotein synthesis[167]. Apolipoprotein B synthesis is developmentally regulated: fetal intestine synthesizes only apoB-100 at 11 wk, but both apo-48 and apo-B100 are synthesized at 16 wk, with apoB-46 being predominant in the mature intestine.

Pinocytosis of lipid globules is important after birth. The immature rat intestine is also able to absorb fatty acids and cholesterol[168]. Triglycerides (TG) are digested by gastric and lingual lipases into fatty acids and 2-monoacylglycerols, and their uptake is higher in the immature intestine than in adults[168,169]. Fatty acid binding proteins on the BBM are present in adults[170]. Lipid uptake is thought to be passive in sucklings (Meddings and Theisen, 1989). Once taken up into the enterocytes, lipids are resynthesized into TG, phospholipids (PL) and cholesterol esters (CE)[171].

Bile acids include solubilizing lipids in the intestinal lumen, which facilitate their diffusion through the intestinal unstirred water layer external to the BBM. Intestinal bile acid uptake is an important step in the enterohepatic circulation of bile acids (recently reviewed in Kullak-Ublick *et al*[172], and this uptake is therefore important in the overall process of lipid absorption. Bile acid transporters are curiously absent during suckling when fat intake is high and when bile acid secretion and recycling would be expected to be maximal. It is speculated that the malabsorption may allow bile acids to enter the colon and affect the development of the enteric flora. It is likely that passive absorption of bile acids during the suckling period may be the mechanism by which bile acids are recirculated[172].

Sodium-dependent bile acid transporters in the BBM or cytosol are detected in the rat at weaning[173,174]. Abrupt increases in bile acid transport at weaning occur in rat and human ileum, and are due to parallel increases in the steady state mRNA abundance and transporter number[175,176].

CONCLUSION

Thus, the ontogeny, early growth and development of the intestine is important for the adult gastroenterologist to appreciate, because of the potential for these early life events to affect the responsiveness of the intestine to physiological or pathological challenges in later life.

REFERENCES

1 **Scoville DH**, Sato T, He XC, Li L. Current view: intestinal stem cells and signaling. *Gastroenterology* 2008; **134**: 849-864
2 **de Santa Barbara P**, van den Brink GR, Roberts DJ. Development and differentiation of the intestinal epithelium. *Cell Mol Life Sci* 2003; **60**: 1322-1332
3 **Bitgood MJ**, McMahon AP. Hedgehog and Bmp genes are coexpressed at many diverse sites of cell-cell interaction in the mouse embryo. *Dev Biol* 1995; **172**: 126-138
4 **van de Wetering M**, Sancho E, Verweij C, de Lau W, Oving I, Hurlstone A, van der Horn K, Batlle E, Coudreuse D, Haramis AP, Tjon-Pon-Fong M, Moerer P, van den Born M, Soete G, Pals S, Eilers M, Medema R, Clevers H. The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. *Cell* 2002; **111**: 241-250
5 **Batlle E**, Henderson JT, Beghtel H, van den Born MM, Sancho E, Huls G, Meeldijk J, Robertson J, van de Wetering M, Pawson T, Clevers H. Beta-catenin and TCF mediate cell positioning in the intestinal epithelium by controlling the expression of EphB/ephrinB. *Cell* 2002; **111**: 251-263
6 **Cully M**, You H, Levine AJ, Mak TW. Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis. *Nat Rev Cancer* 2006; **6**: 184-192
7 **Montgomery RK**, Mulberg AE, Grand RJ. Development of the human gastrointestinal tract: twenty years of progress. *Gastroenterology* 1999; **116**: 702-731
8 **Colony PC**. Successive phases of human fetal intestinal development. In: Kretchmer N, Miinkowski A, editors. Nutritional adaptation of the gastrointestinal tract of the newborn. New York: Vevey/Raven Press, 1983: 3-28
9 **Neu J**, Koldovsky O. Nutrient absorption in the preterm neonate. *Clin Perinatol* 1996; **23**: 229-243

10 **Hirano S**, Kataoka K. Histogenesis of the mouse jejunal mucosa, with special reference to proliferative cells and absorptive cells. *Arch Histol Jpn* 1986; **49**: 333-348
11 **Foltzer-Jourdainne C**, Kedinger M, Raul F. Perinatal expression of brush-border hydrolases in rat colon: hormonal and tissue regulations. *Am J Physiol* 1989; **257**: G496-G503
12 **Lacroix B**, Kedinger M, Simon-Assmann P, Rousset M, Zweibaum A, Haffen K. Developmental pattern of brush border enzymes in the human fetal colon. Correlation with some morphogenetic events. *Early Hum Dev* 1984; **9**: 95-103
13 **Zweibaum A**, Hauri HP, Sterchi E, Chantret I, Haffen K, Bamat J, Sordat B. Immunohistological evidence, obtained with monoclonal antibodies, of small intestinal brush border hydrolases in human colon cancers and foetal colons. *Int J Cancer* 1984; **34**: 591-598
14 **Vidrich A**, Buzan JM, Brodrick B, Ilo C, Bradley L, Fendig KS, Sturgill T, Cohn SM. Fibroblast growth factor receptor-3 regulates Paneth cell lineage allocation and accrual of epithelial stem cells during murine intestinal development. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G168-G178
15 **Holnthoner W**, Pillinger M, Groger M, Wolff K, Ashton AW, Albanese C, Neumeister P, Pestell RG, Petzelbauer P. Fibroblast growth factor-2 induces Lef/Tcf-dependent transcription in human endothelial cells. *J Biol Chem* 2002; **277**: 45847-45853
16 **Winton DJ**, Ponder BA. Stem-cell organization in mouse small intestine. *Proc Biol Sci* 1990; **241**: 13-18
17 **Duncan SA**, Manova K, Chen WS, Hoodless P, Weinstein DC, Bachvarova RF, Darnell JE Jr. Expression of transcription factor HNF-4 in the extraembryonic endoderm, gut, and nephrogenic tissue of the developing mouse embryo: HNF-4 is a marker for primary endoderm in the implanting blastocyst. *Proc Natl Acad Sci USA* 1994; **91**: 7598-7602
18 **Babeu JP**, Darsigny M, Lussier CR, Boudreau F. Hepatocyte nuclear factor 4alpha contributes to an intestinal epithelial phenotype in vitro and plays a partial role in mouse intestinal epithelium differentiation. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G124-G134
19 **Taraviras S**, Mantamadiotis T, Dong-Si T, Mincheva A, Lichter P, Drewes T, Ryffel GU, Monaghan AP, Schütz G. Primary structure, chromosomal mapping, expression and transcriptional activity of murine hepatocyte nuclear factor 4gamma. *Biochim Biophys Acta* 2000; **1490**: 21-32
20 **Archer A**, Sauvaget D, Chauffeton V, Bouchet PE, Chambaz J, Pinçon-Raymond M, Cardot P, Ribeiro A, Lacasa M. Intestinal apolipoprotein A-IV gene transcription is controlled by two hormone-responsive elements: a role for hepatic nuclear factor-4 isoforms. *Mol Endocrinol* 2005; **19**: 2320-2334
21 **Klapper M**, Böhme M, Nitz I, Döring F. The human intestinal fatty acid binding protein (hFABP2) gene is regulated by HNF-4alpha. *Biochem Biophys Res Commun* 2007; **356**: 147-152
22 **Olsen L**, Bressendorff S, Troelsen JT, Olsen J. Differentiation-dependent activation of the human intestinal alkaline phosphatase promoter by HNF-4 in intestinal cells. *Am J Physiol Gastrointest Liver Physiol* 2005; **289**: G220-G226
23 **Rowley CW**, Staloch LJ, Divine JK, McCaul SP, Simon TC. Mechanisms of mutual functional interactions between HNF-4alpha and HNF-1alpha revealed by mutations that cause maturity onset diabetes of the young. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G466-G475
24 **Burke KT**, Horn PS, Tso P, Heubi JE, Woollett LA. Hepatic bile acid metabolism in the neonatal hamster: expansion of the bile acid pool parallels increased Cyp7a1 expression levels. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G144-G151
25 **Russell DW**, Setchell KD. Bile acid biosynthesis. *Biochemistry* 1992; **31**: 4737-4749
26 **Boehm G**, Braun W, Moro G, Minoli I. Bile acid concentrations in serum and duodenal aspirates of healthy preterm infants: effects of gestational and postnatal age. *Biol Neonate* 1997; **71**: 207-214
27 **Heubi JE**, Balistreri WF, Suchy FJ. Bile salt metabolism in the first year of life. *J Lab Clin Med* 1982; **100**: 127-136
28 **De Plaen IG**, Liu SX, Tian R, Neequaye I, May MJ, Han XB, Hsueh W, Jilling T, Lu J, Caplan MS. Inhibition of nuclear factor-kappaB ameliorates bowel injury and prolongs survival in a neonatal rat model of necrotizing enterocolitis. *Pediatr Res* 2007; **61**: 716-721
29 **Liu Y**, Zhu L, Fatheree NY, Liu X, Pacheco SE, Tatevian N, Rhoads JM. Changes in intestinal Toll-like receptors and cytokines precede histological injury in a rat model of necrotizing enterocolitis. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G442-G450
30 **Bajwa PJ**, Lee JW, Straus DS, Lytle C. Activation of PPARgamma by rosiglitazone attenuates intestinal Cl- secretion. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G82-G89
31 **Chen L**, Bush CR, Necela BM, Su W, Yanagisawa M, Anastasiadis PZ, Fields AP, Thompson EA. RS5444, a novel PPARgamma agonist, regulates aspects of the differentiated phenotype in nontransformed intestinal epithelial cells. *Mol Cell Endocrinol* 2006; **251**: 17-32
32 **Drori S**, Girnun GD, Tou L, Szwaya JD, Mueller E, Xia K, Shivdasani RA, Spiegelman BM. Hic-5 regulates an epithelial program mediated by PPARgamma. *Genes Dev* 2005; **19**: 362-375
33 **Thompson EA**. PPARgamma physiology and pathology in gastrointestinal epithelial cells. *Mol Cells* 2007; **24**: 167-176
34 **Moxey PC**, Trier JS. Specialized cell types in the human fetal small intestine. *Anat Rec* 1978; **191**: 269-285
35 **Roth KA**, Hermiston ML, Gordon JI. Use of transgenic mice to infer the biological properties of small intestinal stem cells and to examine the lineage relationships of their descendants. *Proc Natl Acad Sci USA* 1991; **88**: 9407-9411
36 **Simon TC**, Gordon JI. Intestinal epithelial cell differentiation: new insights from mice, flies and nematodes. *Curr Opin Genet Dev* 1995; **5**: 577-586
37 **Podolsky DK**. Regulation of intestinal epithelial proliferation: a few answers, many questions. *Am J Physiol* 1993; **264**: G179-G186
38 **Lovshin J**, Drucker DJ. Synthesis, secretion and biological actions of the glucagon-like peptides. *Pediatr Diabetes* 2000; **1**: 49-57
39 **Murphy BE**. Ontogeny of cortisol-cortisone interconversion in human tissues: a role for cortisone in human fetal development. *J Steroid Biochem* 1981; **14**: 811-817
40 **Marti A**, Fernandez-Otero MP. Prostaglandin E2 accelerates enzymatic and morphological maturation of the small intestine in suckling rats. *Biol Neonate* 1994; **65**: 119-125
41 **McDonald MC**, Henning SJ. Synergistic effects of thyroxine and dexamethasone on enzyme ontogeny in rat small intestine. *Pediatr Res* 1992; **32**: 306-311
42 **Winter HS**, Hendren RB, Fox CH, Russell GJ, Perez-Atayde A, Bhan AK, Folkman J. Human intestine matures as nude mouse xenograft. *Gastroenterology* 1991; **100**: 89-98
43 **Savidge TC**, Morey AL, Ferguson DJ, Fleming KA, Shmakov AN, Phillips AD. Human intestinal development in a severe-combined immunodeficient xenograft model. *Differentiation* 1995; **58**: 361-371
44 **Montgomery RK**, Sybicki MA, Grand RJ. Autonomous biochemical and morphological differentiation in fetal rat intestine transplanted at 17 and 20 days of gestation. *Dev Biol* 1981; **87**: 76-84
45 **Stanton BR**, Perkins AS, Tessarollo L, Sassoon DA, Parada LF. Loss of N-myc function results in embryonic lethality and failure of the epithelial component of the embryo to develop. *Genes Dev* 1992; **6**: 2235-2247

46 **Ang SL**, Rossant J. HNF-3 beta is essential for node and notochord formation in mouse development. *Cell* 1994; **78**: 561-574
47 **Weinstein DC**, Ruiz i Altaba A, Chen WS, Hoodless P, Prezioso VR, Jessell TM, Darnell JE Jr. The winged-helix transcription factor HNF-3 beta is required for notochord development in the mouse embryo. *Cell* 1994; **78**: 575-588
48 **Suh E**, Chen L, Taylor J, Traber PG. A homeodomain protein related to caudal regulates intestine-specific gene transcription. *Mol Cell Biol* 1994; **14**: 7340-7351
49 **Roberts DJ**, Johnson RL, Burke AC, Nelson CE, Morgan BA, Tabin C. Sonic hedgehog is an endodermal signal inducing Bmp-4 and Hox genes during induction and regionalization of the chick hindgut. *Development* 1995; **121**: 3163-3174
50 **Roberts DJ**, Smith DM, Goff DJ, Tabin CJ. Epithelial-mesenchymal signaling during the regionalization of the chick gut. *Development* 1998; **125**: 2791-2801
51 **Basora N**, Vachon PH, Herring-Gillam FE, Perreault N, Beaulieu JF. Relation between integrin alpha7Bbeta1 expression in human intestinal cells and enterocytic differentiation. *Gastroenterology* 1997; **113**: 1510-1521
52 **Rao M**, Manishen WJ, Maheshwari Y, Sykes DE, Siyanova EY, Tyner AL, Weiser MM. Laminin receptor expression in rat intestine and liver during development and differentiation. *Gastroenterology* 1994; **107**: 764-772
53 **Sanderson IR**, Ezzell RM, Kedinger M, Erlanger M, Xu ZX, Pringault E, Leon-Robine S, Louvard D, Walker WA. Human fetal enterocytes in vitro: modulation of the phenotype by extracellular matrix. *Proc Natl Acad Sci USA* 1996; **93**: 7717-7722
54 **Hynes RO**. Targeted mutations in cell adhesion genes: what have we learned from them? *Dev Biol* 1996; **180**: 402-412
55 **Seetharam B**, Yeh KY, Moog F, Alpers DH. Development of intestinal brush border membrane proteins in the rat. *Biochim Biophys Acta* 1977; **470**: 424-436
56 **Vaeth GF**, Henning SJ. Postnatal development of peptidase enzymes in rat small intestine. *J Pediatr Gastroenterol Nutr* 1982; **1**: 111-117
57 **Martin GR**, Henning SJ. Enzymic development of the small intestine: are glucocorticoids necessary? *Am J Physiol* 1984; **246**: G695-G699
58 **Leeper LL**, Henning SJ. Development and tissue distribution of sucrase-isomaltase mRNA in rats. *Am J Physiol* 1990; **258**: G52-G58
59 **Montgomery RK**, Büller HA, Rings EH, Grand RJ. Lactose intolerance and the genetic regulation of intestinal lactase-phlorizin hydrolase. *FASEB J* 1991; **5**: 2824-2832
60 **Goda T**, Yasutake H, Tanaka T, Takase S. Lactase-phlorizin hydrolase and sucrase-isomaltase genes are expressed differently along the villus-crypt axis of rat jejunum. *J Nutr* 1999; **129**: 1107-1113
61 **Lacroix B**, Kedinger M, Simon-Assmann P, Haffen K. Early organogenesis of human small intestine: scanning electron microscopy and brush border enzymology. *Gut* 1984; **25**: 925-930
62 **Villa M**, Ménard D, Semenza G, Mantei N. The expression of lactase enzymatic activity and mRNA in human fetal jejunum. Effect of organ culture and of treatment with hydrocortisone. *FEBS Lett* 1992; **301**: 202-206
63 **Escher JC**, de Koning ND, van Engen CG, Arora S, Büller HA, Montgomery RK, Grand RJ. Molecular basis of lactase levels in adult humans. *J Clin Invest* 1992; **89**: 480-483
64 **Wang Y**, Harvey C, Rousset M, Swallow DM. Expression of human intestinal mRNA transcripts during development: analysis by a semiquantitative RNA polymerase chain reaction method. *Pediatr Res* 1994; **36**: 514-521
65 **Fajardo O**, Naim HY, Lacey SW. The polymorphic expression of lactase in adults is regulated at the messenger RNA level. *Gastroenterology* 1994; **106**: 1233-1241
66 **Troelsen JT**, Mitchelmore C, Spodsberg N, Jensen AM, Norén O, Sjöström H. Regulation of lactase-phlorizin hydrolase gene expression by the caudal-related homoeodomain protein Cdx-2. *Biochem J* 1997; **322** (Pt 3): 833-838
67 **Mitchelmore C**, Troelsen JT, Sjöström H, Norén O. The HOXC11 homeodomain protein interacts with the lactase-phlorizin hydrolase promoter and stimulates HNF1alpha-dependent transcription. *J Biol Chem* 1998; **273**: 13297-13306
68 **Fitzgerald K**, Bazar L, Avigan MI. GATA-6 stimulates a cell line-specific activation element in the human lactase promoter. *Am J Physiol* 1998; **274**: G314-G324
69 **Galand G**. Brush border membrane sucrase-isomaltase, maltase-glucoamylase and trehalase in mammals. Comparative development, effects of glucocorticoids, molecular mechanisms, and phylogenetic implications. *Comp Biochem Physiol B* 1989; **94**: 1-11
70 **Koldovsky O**. Developmental, dietary and hormonal control of intestinal disaccharidases in mammals (including man). In: Randle PJ, Steiner DF, Whelan WJ, editors. Carbohydrate metabolism and its disorders. London: Academic Press, 1981: 481-522
71 **Büller HA**, Grand RJ. Lactose intolerance. *Annu Rev Med* 1990; **41**: 141-148
72 **Rossi M**, Maiuri L, Fusco MI, Salvati VM, Fuccio A, Auricchio S, Mantei N, Zecca L, Gloor SM, Semenza G. Lactase persistence versus decline in human adults: multifactorial events are involved in down-regulation after weaning. *Gastroenterology* 1997; **112**: 1506-1514
73 **Naim HY**, Lentze MJ. Impact of O-glycosylation on the function of human intestinal lactase-phlorizin hydrolase. Characterization of glycoforms varying in enzyme activity and localization of O-glycoside addition. *J Biol Chem* 1992; **267**: 25494-25504
74 **Danielsen EM**, Skovbjerg H, Norén O, Sjöström H. Biosynthesis of intestinal microvillar proteins. Intracellular processing of lactase-phlorizin hydrolase. *Biochem Biophys Res Commun* 1984; **122**: 82-90
75 **Lottaz D**, Oberholzer T, Bähler P, Semenza G, Sterchi EE. Maturation of human lactase-phlorizin hydrolase. Proteolytic cleavage of precursor occurs after passage through the Golgi complex. *FEBS Lett* 1992; **313**: 270-276
76 **Wüthrich M**, Grünberg J, Hahn D, Jacob R, Radebach I, Naim HY, Sterchi EE. Proteolytic processing of human lactase-phlorizin hydrolase is a two-step event: identification of the cleavage sites. *Arch Biochem Biophys* 1996; **336**: 27-34
77 **Triadou N**, Zweibaum A. Maturation of sucrase-isomaltase complex in human fetal small and large intestine during gestation. *Pediatr Res* 1985; **19**: 136-138
78 **Tung J**, Markowitz AJ, Silberg DG, Traber PG. Developmental expression of SI is regulated in transgenic mice by an evolutionarily conserved promoter. *Am J Physiol* 1997; **273**: G83-G92
79 **Henning SJ**. Ontogeny of enzymes in the small intestine. *Annu Rev Physiol* 1985; **47**: 231-245
80 **Buts JP**, Duranton B, De Keyser N, Sokal EM, Maernhout AS, Raul F, Marandi S. Premature stimulation of rat sucrase-isomaltase (SI) by exogenous insulin and the analog B-Asp10 is regulated by a receptor-mediated signal triggering SI gene transcription. *Pediatr Res* 1998; **43**: 585-591
81 **Sebastio G**, Hunziker W, O'Neill B, Malo C, Ménard D, Auricchio S, Semenza G. The biosynthesis of intestinal sucrase-isomaltase in human embryo is most likely controlled at the level of transcription. *Biochem Biophys Res Commun* 1987; **149**: 830-839
82 **Wu GD**, Chen L, Forslund K, Traber PG. Hepatocyte nuclear factor-1 alpha (HNF-1 alpha) and HNF-1 beta regulate transcription via two elements in an intestine-specific promoter. *J Biol Chem* 1994; **269**: 17080-17085
83 **Naim HY**, Sterchi EE, Lentze MJ. Biosynthesis of the human

sucrase-isomaltase complex. Differential O-glycosylation of the sucrase subunit correlates with its position within the enzyme complex. *J Biol Chem* 1988; **263**: 7242-7253
84 **Fransen JA**, Hauri HP, Ginsel LA, Naim HY. Naturally occurring mutations in intestinal sucrase-isomaltase provide evidence for the existence of an intracellular sorting signal in the isomaltase subunit. *J Cell Biol* 1991; **115**: 45-57
85 **Koldovský O**. Search for role of milk-borne biologically active peptides for the suckling. *J Nutr* 1989; **119**: 1543-1551
86 **Puchal AA**, Buddington RK. Postnatal development of monosaccharide transport in pig intestine. *Am J Physiol* 1992; **262**: G895-G902
87 **Rubin DC**. Spatial analysis of transcriptional activation in fetal rat jejunal and ileal gut epithelium. *Am J Physiol* 1992; **263**: G853-G863
88 **Chabot JG**, Payet N, Hugon JS. Effects of epidermal growth factor (EGF) on adult mouse small intestine in vivo and in organ culture. *Comp Biochem Physiol A Comp Physiol* 1983; **74**: 247-252
89 **Chapman JF**, Phillips JC, Rosenthal MA, Herbert WN. Evaluation of the PG-Numeric assay for semi-automated analysis for phosphatidylglycerol in amniotic fluid. *Clin Chem* 1990; **36**: 1974-1977
90 **Mulvihill SJ**, Stone MM, Debas HT, Fonkalsrud EW. The role of amniotic fluid in fetal nutrition. *J Pediatr Surg* 1985; **20**: 668-672
91 **Pritchard JA**. Fetal swallowing and amniotic fluid volume. *Obstet Gynecol* 1966; **28**: 606-610
92 **Bradley RM**, Mistretta CM. Fetal sensory receptors. *Physiol Rev* 1975; **55**: 352-382
93 **Liley AW**. The foetus as a personality. *Aust N Z J Psychiatry* 1972; **6**: 99-105
94 **Buchmiller TL**, Fonkalsrud EW, Kim CS, Chopourian HL, Shaw KS, Lam MM, Diamond JM. Upregulation of nutrient transport in fetal rabbit intestine by transamniotic substrate administration. *J Surg Res* 1992; **52**: 443-447
95 **Trahair JF**, Harding R, Bocking AD, Silver M, Robinson PM. The role of ingestion in the development of the small intestine in fetal sheep. *Q J Exp Physiol* 1986; **71**: 99-104
96 **Pitkin RM**, Reynolds WA. Fetal ingestion and metabolism of amniotic fluid protein. *Am J Obstet Gynecol* 1975; **123**: 356-363
97 **Buddington RK**. Nutrition and ontogenetic development of the intestine. *Can J Physiol Pharmacol* 1994; **72**: 251-259
98 **Buddington RK**, Malo C. Intestinal brush-border membrane enzyme activities and transport functions during prenatal development of pigs. *J Pediatr Gastroenterol Nutr* 1996; **23**: 51-64
99 **Malo C**, Berteloot A. Proximo-distal gradient of Na+-dependent D-glucose transport activity in the brush border membrane vesicles from the human fetal small intestine. *FEBS Lett* 1987; **220**: 201-205
100 **Khan JM**, Wingertzahn MA, Teichberg S, Vancurova I, Harper RG, Wapnir RA. Development of the intestinal SGLT1 transporter in rats. *Mol Genet Metab* 2000; **69**: 233-239
101 **Shu R**, David ES, Ferraris RP. Dietary fructose enhances intestinal fructose transport and GLUT5 expression in weaning rats. *Am J Physiol* 1997; **272**: G446-G453
102 **Malo C**. Kinetic evidence for heterogeneity in Na+-D-glucose cotransport systems in the normal human fetal small intestine. *Biochim Biophys Acta* 1988; **938**: 181-188
103 **Malo C**. Separation of two distinct Na+/D-glucose cotransport systems in the human fetal jejunum by means of their differential specificity for 3-O-methylglucose. *Biochim Biophys Acta* 1990; **1022**: 8-16
104 **Kellett GL**, Helliwell PA. The diffusive component of intestinal glucose absorption is mediated by the glucose-induced recruitment of GLUT2 to the brush-border membrane. *Biochem J* 2000; **350** Pt 1: 155-162
105 **Davidson NO**, Hausman AM, Ifkovits CA, Buse JB, Gould GW, Burant CF, Bell GI. Human intestinal glucose transporter expression and localization of GLUT5. *Am J Physiol* 1992; **262**: C795-C800
106 **Matsumoto K**, Takao Y, Akazawa S, Yano M, Uotani S, Kawasaki E, Takino H, Yamasaki H, Okuno S, Yamaguchi Y. Developmental change of facilitative glucose transporter expression in rat embryonal and fetal intestine. *Biochem Biophys Res Commun* 1993; **193**: 1275-1282
107 **Cui XL**, Jiang L, Ferraris RP. Regulation of rat intestinal GLUT2 mRNA abundance by luminal and systemic factors. *Biochim Biophys Acta* 2003; **1612**: 178-185
108 **Cherbuy C**, Darcy-Vrillon B, Posho L, Vaugelade P, Morel MT, Bernard F, Leturque A, Penicaud L, Duée PH. GLUT2 and hexokinase control proximodistal gradient of intestinal glucose metabolism in the newborn pig. *Am J Physiol* 1997; **272**: G1530-G1539
109 **Smith MW**. Expression of digestive and absorptive function in differentiating enterocytes. *Annu Rev Physiol* 1985; **47**: 247-260
110 **Barfull A**, Garriga C, Mitjans M, Planas JM. Ontogenetic expression and regulation of Na(+)-D-glucose cotransporter in jejunum of domestic chicken. *Am J Physiol Gastrointest Liver Physiol* 2002; **282**: G559-G564
111 **Rouwet EV**, Heineman E, Buurman WA, ter Riet G, Ramsay G, Blanco CE. Intestinal permeability and carrier-mediated monosaccharide absorption in preterm neonates during the early postnatal period. *Pediatr Res* 2002; **51**: 64-70
112 **Morikawa Y**, Fujimoto K, Okada T. Morphometrical changes in the apical surface of the colonic absorptive cells in perinatal rats with special reference to the effect of fetal oral administration of milk in utero. *Lab Anim* 1991; **25**: 242-246
113 **Vagnerová R**, Kubínová L, Pácha J. Correlation of function and structure in developing rat distal colon. *Cell Tissue Res* 1997; **288**: 95-99
114 **Schwarz SM**, Bostwick HE, Danziger MD, Newman LJ, Medow MS. Ontogeny of basolateral membrane lipid composition and fluidity in small intestine. *Am J Physiol* 1989; **257**: G138-G144
115 **Schwarz SM**, Ling SD, Hostetler B, Draper JP, Watkins JB. Lipid composition and membrane fluidity in the small intestine of the developing rabbit. *Gastroenterology* 1984; **86**: 1544-1551
116 **Catassi C**, Bonucci A, Coppa GV, Carlucci A, Giorgi PL. Intestinal permeability changes during the first month: effect of natural versus artificial feeding. *J Pediatr Gastroenterol Nutr* 1995; **21**: 383-386
117 **Castelló A,** Gumá A, Sevilla L, Furriols M, Testar X, Palacín M, Zorzano A. Regulation of GLUT5 gene expression in rat intestinal mucosa: regional distribution, circadian rhythm, perinatal development and effect of diabetes. *Biochem J* 1995; **309** (Pt 1): 271-277
118 **Rand EB**, Depaoli AM, Davidson NO, Bell GI, Burant CF. Sequence, tissue distribution, and functional characterization of the rat fructose transporter GLUT5. *Am J Physiol* 1993; **264**: G1169-G1176
119 **Toloza EM**, Diamond J. Ontogenetic development of nutrient transporters in rat intestine. *Am J Physiol* 1992; **263**: G593-G604
120 **Char VC**, Rudolph AM. Digestion and absorption of carbohydrates by the fetal lamb in utero. *Pediatr Res* 1979; **13**: 1018-1023
121 **Shu R**, David ES, Ferraris RP. Luminal fructose modulates fructose transport and GLUT-5 expression in small intestine of weaning rats. *Am J Physiol* 1998; **274**: G232-G239
122 **Jiang L**, Ferraris RP. Developmental reprogramming of rat GLUT-5 requires de novo mRNA and protein synthesis. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G113-G120
123 **Hoekstra JH**, van Kempen AA, Bijl SB, Kneepkens CM. Fructose breath hydrogen tests. *Arch Dis Child* 1993; **68**: 136-138

124 **Choi YK**, Johlin FC Jr, Summers RW, Jackson M, Rao SS. Fructose intolerance: an under-recognized problem. *Am J Gastroenterol* 2003; **98**: 1348-1353
125 **Younoszai MK**, Lynch A. In vivo D-glucose absorption in the developing rat small intestine. *Pediatr Res* 1975; **9**: 130-133
126 **Navab F**, Winter CG. Effect of aging on intestinal absorption of aromatic amino acids in vitro in the rat. *Am J Physiol* 1988; **254**: G631-G636
127 **Himukai M**, Konno T, Hoshi T. Age-dependent change in intestinal absorption of dipeptides and their constituent amino acids in the guinea pig. *Pediatr Res* 1980; **14**: 1272-1275
128 **Guandalini S**, Rubino A. Development of dipeptide transport in the intestinal mucosa of rabbits. *Pediatr Res* 1982; **16**: 99-103
129 **Buddington RK**, Diamond JM. Ontogenetic development of intestinal nutrient transporters. *Annu Rev Physiol* 1989; **51**: 601-619
130 **Malo C**. Multiple pathways for amino acid transport in brush border membrane vesicles isolated from the human fetal small intestine. *Gastroenterology* 1991; **100**: 1644-1652
131 **Lebenthal A**, Lebenthal E. The ontogeny of the small intestinal epithelium. *JPEN J Parenter Enteral Nutr* 1999; **23**: S3-S6
132 **Rome S**, Barbot L, Windsor E, Kapel N, Tricottet V, Huneau JF, Reynes M, Gobert JG, Tomé D. The regionalization of PepT1, NBAT and EAAC1 transporters in the small intestine of rats are unchanged from birth to adulthood. *J Nutr* 2002; **132**: 1009-1011
133 **Moriyama IS**. [Development of fetal organs and adaptation to extrauterine life] *Nippon Sanka Fujinka Gakkai Zasshi* 1986; **38**: 1227-1237
134 **Israel EJ**, Taylor S, Wu Z, Mizoguchi E, Blumberg RS, Bhan A, Simister NE. Expression of the neonatal Fc receptor, FcRn, on human intestinal epithelial cells. *Immunology* 1997; **92**: 69-74
135 **Udall JN**, Bloch KJ, Vachino G, Feldman P, Walker WA. Development of the gastrointestinal mucosal barrier. IV. The effect of inhibition of proteolysis on the uptake of macromolecules by the intestine of the newborn rabbit before and after weaning. *Biol Neonate* 1984; **45**: 289-295
136 **Jakoi ER**, Cambier J, Saslow S. Transepithelial transport of maternal antibody: purification of IgG receptor from newborn rat intestine. *J Immunol* 1985; **135**: 3360-3364
137 **Martín MG**, Wu SV, Walsh JH. Ontogenetic development and distribution of antibody transport and Fc receptor mRNA expression in rat intestine. *Dig Dis Sci* 1997; **42**: 1062-1069
138 **Teichberg S**, Isolauri E, Wapnir RA, Roberts B, Lifshitz F. Development of the neonatal rat small intestinal barrier to nonspecific macromolecular absorption: effect of early weaning to artificial diets. *Pediatr Res* 1990; **28**: 31-37
139 **Jakobsson I**, Lindberg T, Lothe L, Axelsson I, Benediktsson B. Human alpha-lactalbumin as a marker of macromolecular absorption. *Gut* 1986; **27**: 1029-1034
140 **Vukavić T**. Timing of the gut closure. *J Pediatr Gastroenterol Nutr* 1984; **3**: 700-703
141 **Thomson AB**, Keelan M. The aging gut. *Can J Physiol Pharmacol* 1986; **64**: 30-38
142 **Lebenthal E**, Lee PC. Development of functional responses in human exocrine pancreas. *Pediatrics* 1980; **66**: 556-560
143 **Lindberg T**. Intestinal dipeptidases: characterization, development and distribution of intestinal dipeptidases of the human foetus. *Clin Sci* 1966; **30**: 505-515
144 **Sevenhuysen GP**, Holodinsky C, Dawes C. Development of salivary alpha-amylase in infants from birth to 5 months. *Am J Clin Nutr* 1984; **39**: 584-588
145 **Dewit O**, Dibba B, Prentice A. Breast-milk amylase activity in English and Gambian mothers: effects of prolonged lactation, maternal parity, and individual variations. *Pediatr Res* 1990; **28**: 502-506
146 **Lee PC**, Kim OK, Lebenthal E. Effect of early weaning and prolonged nursing on development of the rat pancreas. *Pediatr Res* 1982; **16**: 470-473
147 **Cleghorn G**, Durie P, Benjamin L, Dati F. The ontogeny of serum immunoreactive pancreatic lipase and cationic trypsinogen in the premature human infant. *Biol Neonate* 1988; **53**: 10-16
148 **Hamosh M**, Scanlon JW, Ganot D, Likel M, Scanlon KB, Hamosh P. Fat digestion in the newborn. Characterization of lipase in gastric aspirates of premature and term infants. *J Clin Invest* 1981; **67**: 838-846
149 **Sheldon W**. Congenital pancreatic lipase deficiency. *Arch Dis Child* 1964; **39**: 268-271
150 **Alemi B**, Hamosh M, Scanlon JW, Salzman-Mann C, Hamosh P. Fat digestion in very low-birth-weight infants: effect of addition of human milk to low-birth-weight formula. *Pediatrics* 1981; **68**: 484-489
151 **Hernell O**, Bläckberg L, Bernbäck S. Digestion of human milk fat in early infancy. *Acta Paediatr Scand Suppl* 1989; **351**: 57-62
152 **Boehm G**, Borte M, Müller H, Moro G, Minoli I. Activities of trypsin and lipase in duodenal aspirates of preterm infants: influence of dietary protein and fat composition. *Am J Clin Nutr* 1995; **61**: 524-527
153 **Rings EH**, Minich DM, Vonk RJ, Stellaard F, Fetter WP, Verkade HJ. Functional development of fat absorption in term and preterm neonates strongly correlates with ability to absorb long-chain Fatty acids from intestinal lumen. *Pediatr Res* 2002; **51**: 57-63
154 **Thomson AB**, Keelan M, Garg M, Clandinin MT. Evidence for critical-period programming of intestinal transport function: variations in the dietary ratio of polyunsaturated to saturated fatty acids alters ontogeny of the rat intestine. *Biochim Biophys Acta* 1989; **1001**: 302-315
155 **Perin NM**, Clandinin T, Thomson AB. Importance of milk and diet on the ontogeny and adaptation of the intestine. *J Pediatr Gastroenterol Nutr* 1997; **24**: 419-425
156 **Jarocka-Cyrta E**, Perin N, Keelan M, Wierzbicki E, Wierzbicki T, Clandinin MT, Thomson AB. Early dietary experience influences ontogeny of intestine in response to dietary lipid changes in later life. *Am J Physiol* 1998; **275**: G250-G258
157 **Karasov WH**, Solberg DH, Chang SD, Hughes M, Stein ED, Diamond JM. Is intestinal transport of sugars and amino acids subject to critical-period programming? *Am J Physiol* 1985; **249**: G770-G785
158 **Lucas A**. Programming by early nutrition: an experimental approach. *J Nutr* 1998; **128**: 401S-406S
159 **Lucas A**. Programming not metabolic imprinting. *Am J Clin Nutr* 2000; **71**: 602
160 **Barker DJ**, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993; **341**: 938-941
161 **Seckl J**. Mechanisms of fetal origins of health problems in adults need to be investigated. *BMJ* 1998; **317**: 210
162 **Bell RC**, Hoedl A, Turchinsky J. Fructose feeding in the suckling-weaning transition in rats: effects on hyperlipidemia in adulthood. *Arch Physiol Biochem* 2003; **111**: 17-22
163 **Keelan M**, Thomson AB, Garg ML, Clandinin MT. Critical period programming of intestinal glucose transport via alterations in dietary fatty acid composition. *Can J Physiol Pharmacol* 1990; **68**: 642-645
164 **Thomson AB**, Keelan M. Late effects of early feeding of a low cholesterol diet on the intestinal active and passive transport properties in the rabbit. *Mech Ageing Dev* 1987; **40**: 157-170
165 **Perin N**, Jarocka-Cyrta E, Keelan M, Clandinin T, Thomson A. Dietary lipid composition modifies intestinal morphology and nutrient transport in young rats. *J Pediatr Gastroenterol Nutr* 1999; **28**: 46-53

166 **Perin N**, Keelan M, Jarocka-Cyrta E, Clandinin MT, Thomson AB. Ontogeny of intestinal adaptation in rats in response to isocaloric changes in dietary lipids. *Am J Physiol* 1997; **273**: G713-G720
167 **Thibault L**, Ménard D, Loirdighi N, Levy E. Ontogeny of intestinal lipid and lipoprotein synthesis. *Biol Neonate* 1992; **62**: 100-107
168 **Meddings JB**, Theisen S. Development of rat jejunum: lipid permeability, physical properties, and chemical composition. *Am J Physiol* 1989; **256**: G931-G940
169 **Flores CA**, Hing SA, Wells MA, Koldovský O. Rates of triolein absorption in suckling and adult rats. *Am J Physiol* 1989; **257**: G823-G829
170 **Agellon LB**, Toth MJ, Thomson AB. Intracellular lipid binding proteins of the small intestine. *Mol Cell Biochem* 2002; **239**: 79-82
171 **Shiau YF**, Umstetter C, Kendall K, Koldovsky O. Development of fatty acid esterification mechanisms in rat small intestine. *Am J Physiol* 1979; **237**: E399-E403
172 **Kullak-Ublick GA**, Stieger B, Meier PJ. Enterohepatic bile salt transporters in normal physiology and liver disease. *Gastroenterology* 2004; **126**: 322-342
173 **Stahl GE**, Mascarenhas MR, Fayer JC, Shiau YF, Watkins JB. Passive jejunal bile salt absorption alters the enterohepatic circulation in immature rats. *Gastroenterology* 1993; **104**: 163-173
174 **Christie DM**, Dawson PA, Thevananther S, Shneider BL. Comparative analysis of the ontogeny of a sodium-dependent bile acid transporter in rat kidney and ileum. *Am J Physiol* 1996; **271**: G377-G385
175 **Little JM**, Lester R. Ontogenesis of intestinal bile salt absorption in the neonatal rat. *Am J Physiol* 1980; **239**: G319-G323
176 **Barnard JA**, Ghishan FK, Wilson FA. Ontogenesis of taurocholate transport by rat ileal brush border membrane vesicles. *J Clin Invest* 1985; **75**: 869-873

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