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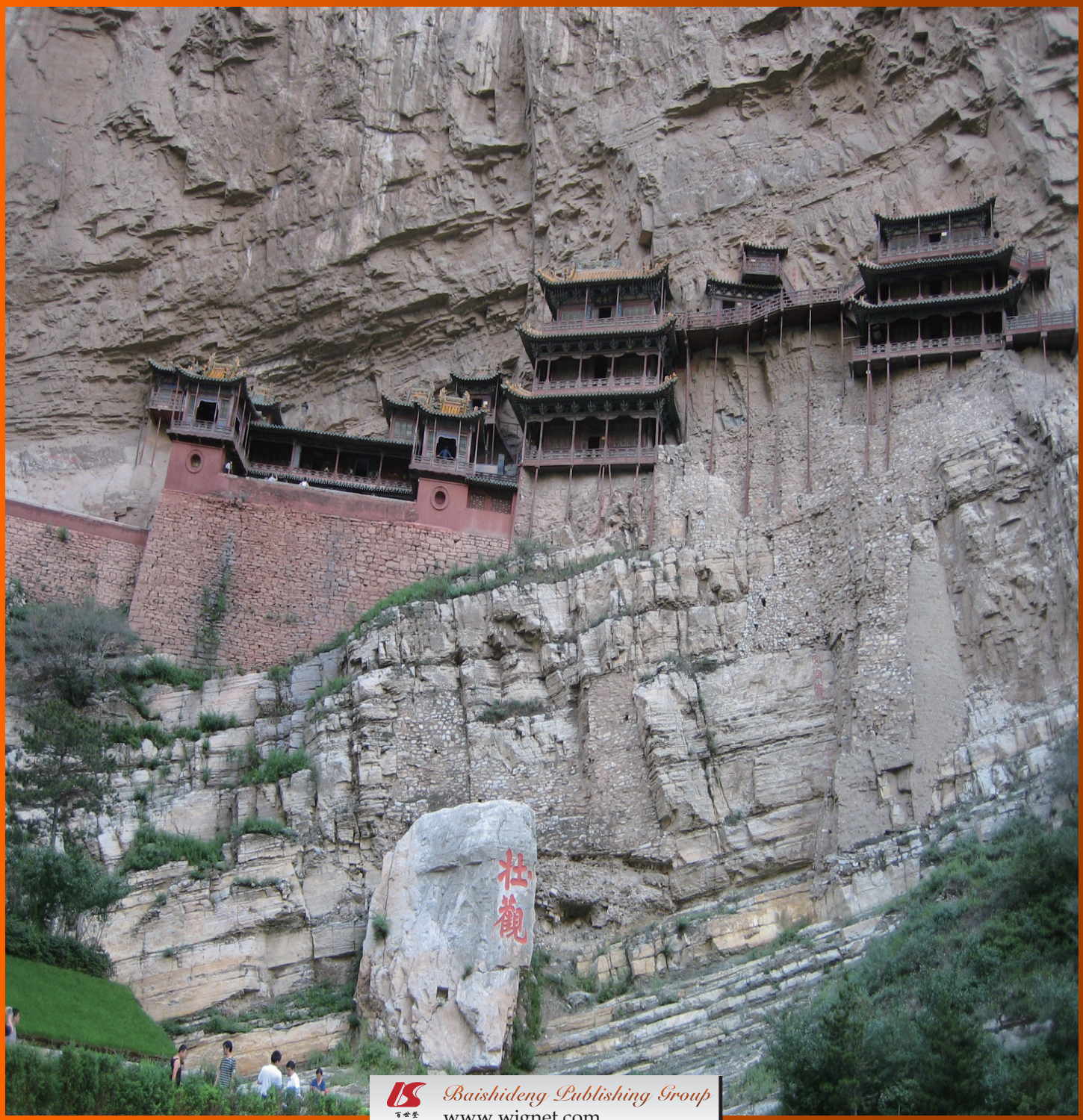

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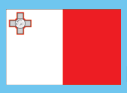

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August 23, 2008
Photograph by Li Ma
Shanxi Province, China
Located at the foot of Mt. Hengshan in China's Shanxi Province, the Suspended Temple is nestled in the steep precipices and cliffs of Cuiping Peak west of Jinlong Gorge. The temple was built among the cliffs, suspended in midair.

AIM AND SCOPE

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TOPIC HIGHLIGHT

Didier Vieau, Professor, *Series Editor*

Nutritional programming of pancreatic β-cell plasticity

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Abstract

Nutritional insufficiency during pregnancy has been shown to alter the metabolism of the offspring and can increase the risk of type 2 diabetes. The phenotype in the offspring involves changes to the morphology and functional capacity of the endocrine pancreas, and in the supporting islet microvasculature. Pancreatic β-cells possess a plastic potential and can partially recover from catastrophic loss. This is partly due to the existence of progenitors within the islets and the ability to generate new islets by neogenesis from the pancreatic ducts. This regenerative capacity is induced by bone marrow-derived stem cells, including endothelial cell progenitors and is associated with increased angiogenesis within the islets. Nutritional insults in early life, such as feeding a low protein diet to the mother, impair the regenerative capacity of the β-cells. The mechanisms underlying this include a reduced ability of β-cells to differentiate from the progenitor population, changes in the inductive signals from the microvasculature and an altered presence of endothelial progenitors. Statin treatment within animal models was associated with angiogenesis in the islet microvasculature, improved vascular function and an increase in β-cell mass. This demonstrates that reversal of the impaired β-cell phenotype observed following nutritional insult in early life is potentially possible.

Key words: Islet; β-cell; Plasticity; Diabetes; Nutrition; Statin

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INTRODUCTION

Epidemiological studies have demonstrated that dietary restriction during pregnancy results in a reduced birth weight[1], leading to permanent changes in organ development, including the endocrine pancreas[2] and contributing to an adult predisposition to several chronic disease conditions, including type 2 diabetes and cardiovascular disease. Using an established model of dietary protein restriction during pregnancy and lactation, it has been extensively reported that dietary insufficiency in early life alters normal pancreatic development, which ultimately contributes to impaired glucose homeostasis in adulthood[3-7]. A low protein (LP) diet given to rats during pregnancy results in reduced β-cell mass (islet size) due to altered cell cycle kinetics and a lower proliferation rate but a greater incidence of apoptosis. The endocrine pancreas demonstrates impaired glucose-stimulated insulin release and greater cytokine-induced cell death. Offspring of LP-fed dams are glucose intolerant by 130 d of age.

However, the nutritional insult early in life not only changes the β-cell phenotype but also has a profound effect on the micro-vasculature of the pancreas. Intra-islet vascular volume and endothelial cell vascular endothelial growth factor (VEGF) receptor abundance were reduced in LP-fed offspring and both were reversed by supplementation of the LP diet with taurine, an amino acid which normally is present at high concentrations within islets but which is depleted in animals exposed to a LP diet[7]. Islet vasculature is also diminished in other models of intrauterine growth retardation such as uterine artery ligation of the mother[8] and in that study, it was reversible by administration of the glucagon-like polypeptide-1 analog, exendin 4, to the offspring, presumably by increasing β-cell-derived VEGF which promoted local angiogenesis. We recently applied the LP diet model to the mouse and found that the β-cell regeneration that normally occurs in juveniles following depletion of β-cell mass with streptozotocin (STZ) treatment was prevented if the offspring had been previously exposed to a LP diet[9]. It is therefore possible that the phenotypic changes seen in the endocrine pancreas as a result of nutritional insult in early life may represent impaired mechanisms of β-cell plasticity and that these relate to deficiencies in islet vasculogenesis. This review explores the capacity for β-cell plasticity, the relationship to the islet microvasculature and how such deficiencies might be reversed to prevent the risk of future diabetes.

DEVELOPMENT OF PANCREATIC β-CELLS

Both islet endocrine cells and acinar tissue develop from pancreatic ductal epithelium during fetal and neonatal development in the rat and human fetus[10,11]. The initial development of both lineages depends on the expression of key transcription factors such as Pdx1 and Ptf1 within the ductal cells[10]. Pdx1 is also required in the mature β-cell where it trans-activates the insulin and GLUT2 gene promoters. Other transcription factors, including neurogenin-3 (Ngn3), β2/NeuroD, Pax-4 and -6, and Nkx2.2, are necessary to complete the differentiation of individual endocrine cell lineages[12]. Pancreatic ductal cells or multipotential stem cells can be manipulated *in vitro* to yield islet-like structures with multiple endocrine cell types[13-15]. The number of these structures can be potentiated by introducing extracellular matrix (ECM)[16], or specific combinations of growth factors such as activin, exendin-4, hepatocyte growth factor (HGF)[17], fibroblast growth factor-1 or leukemia inhibitory factor[18]. Regardless, the yield of new β-cells is generally low, most likely because the optimal environment for β-cell generation requires other supporting cell types.

EVIDENCE OF ENDOGENOUS β-CELL REGENERATION

Plasticity in β-cell mass is a physiological response and is seen during pregnancy[19,20] and with obesity[21]. A delicate balance of proliferation and apoptotic loss maintains β-cell mass *in vivo*. The human fetus and neonatal rodent undergo significant remodeling of their endocrine pancreas involving β-cell proliferation, neogenesis and apoptosis[22]. In humans there is histological evidence of β-cell neogenesis and a regenerative response in children and adolescents with type 1 diabetes[23,24]. Recently, proliferation of remaining β-cells was shown in deceased patients with new onset type 1 diabetes but not in those with long-standing disease or type 2 diabetes[25].

The origins of new β-cells in animal models of regeneration are various. Partial pancreatectomy induced the expansion of both endocrine and exocrine pancreatic mass[26,27], while injection of STZ into young rodents was shown to induce islet neogenesis from the ducts, similar to that occurring in embryogenesis[28]. Pancreatic ductal ligation has been shown to stimulate a doubling of β-cell mass in adult rats[29] by both islet neogenesis and hypertrophy of existing β-cells[30]. Surviving β-cells have been shown to spontaneously proliferate after cessation of their selective doxycycline-induced apoptosis by diphtheria toxin[31], supporting the concept that during regeneration β-cells are released from a tight control of cell replication. However, hormone-negative cells expressing Thy1.1 and CD133 have been identified in adult rat pancreatic ducts that subsequently expressed Pdx1 and both insulin and glucagon[32]. Similar duel insulin and glucagon-expressing cells have been identified in neonatal rat islets during β-cell regeneration following STZ treatment[33] and could represent resident endocrine cell progenitors. Seaberg *et al*[34] showed that multi-potential pancreatic stem cells existed within mouse islets and pancreatic ducts but were extremely rare. Conversely, Dor *et al*[35] and Nir *et al*[36] showed that following partial pancreatectomy, repopulation of β-cells within mouse islets occurred solely by replication of existing β-cells. A number of reports now show this conclusion to be misinterpreted.

Liu *et al*[37] used the same mouse model as Dor *et al*[35], where β-cells were lineage-tagged with human placental alkaline phosphatase (HPAP) to show that β-cell progenitors existed within the islets with little or no insulin expression and that these proliferated following β-cell depletion with STZ. Such cells were in the periphery of the islets and expressed the transcription factor MafB, a marker of immature β-cells. Similarly, Szabat *et al*[38] identified cells in mouse islets that were Pdx1-positive but insulin-negative, and which co-expressed MafB and Nkx2.2. These could mature into insulin-expressing β-cells *in vitro* that expressed MafA and Glut2, or could remain as progenitors. Finally, Thorel *et al*[39] showed that after near-total induced β-cell loss, new β-cells could be generated by trans-differentiation from α-cells. We have utilized the transgenic mouse model of Melton[35], in which approximately 30%-40% of β-cells and their subsequent progeny are genetically tagged with HPAP, to show that neonatal islets can be de-differentiated to a progenitor cell population *in vitro* and subsequently re-differentiated into pseudo-islet structures that express many of the transcription

factor signatures of functional β-cells[40]. HPAP-tagged β-cells contribute both to the de-differentiated and re-differentiated cell populations. In summary, in postnatal life β-cell regeneration seems to predominantly occur within existing islets but may proceed both from a differentiation of resident progenitors and by the proliferation of mature β-cells. Additionally, substantial plasticity exists within existing β-cells, at least *in vitro*, to de-differentiate to a more primitive progenitor phenotype and subsequently to re-differentiate back into endocrine cells.

CONTRIBUTION OF THE MICROVASCULATURE TO β-CELL REGENERATION

Pancreatic islet vascular endothelium can induce β-cell growth, differentiation and function through the actions of paracrine growth factors and through integrin signals across the shared basement membrane[41,42]. Paracrine actions within the islet allow a synthesis of VEGF from the β-cells which contributes to endothelial cell proliferation, while a reciprocal production of HGF by the endothelial cells promotes β-cell growth[43]. We found that administration of STZ in the young rat not only caused a loss of β-cells, but an associated decrease in islet vasculature and that recovery of β-cell mass only occurred subsequent to recovery of the microvasculature[44]. However, the β-cell regenerative environment is likely to include not only vascular endothelium, but also the endothelial precursor cells (EPC)[45], mesenchymal stromal cells and bone marrow-derived hematopoietic lineage stem cells. Understanding how these components contribute to the regenerative environment and their communication with β-cells or their progenitors is key to understanding the control of β-cell regeneration.

BONE MARROW STEM CELLS AND β-CELL REGENERATION

Transplantation of bone marrow progenitor cells was shown by us and others to cause a reversal of hyperglycemia in animal models of diabetes and in newly diagnosed individuals with type 1 diabetes[46-49]. The ability of such cells to selectively home to damaged tissues has been variously linked to their expression of L-selectin[50], β2-integrins[51] and stromal cell-derived factor-1[52]. In some studies, a direct trans-differentiation of bone marrow-derived stem cells into insulin-positive β-cells was demonstrated, either *in vivo* or following *in vitro* lineage manipulation[53-55] but the direct contribution of bone marrow stem cells to new β-cells has generally been found to be low and inconsistent with the resulting increase in insulin secretion and/or normalization of blood glucose[46,56-58]. However, following bone marrow stem cell transfer, islet neovascularization was seen[46,59], accompanied by an increase in endogenous β-cells by replication or neogenesis of new islets from the pancreatic ducts[46,56]. There is debate as to which bone marrow-derived cells 'induce' β-cell regeneration. Yoder *et al*[60] concluded that bone marrow contained both pro-angiogenic hematopoietic progenitors of myeloid/monocyte lineage and true EPC that were not of hematopoietic lineage. Pro-angiogenic hematopoietic progenitors were hypothesized to function as paracrine supportive cells that induced vasculogenesis and tissue regeneration but the majority did not form functional endothelial cells. In the context of β-cell regeneration, these cells would be synergistic to the direct interactions known to occur between vascular endothelium and β-cells. In most papers, pro-angiogenic hematopoietic progenitors and true EPC are not distinguished between and are collectively described as EPC.

An alternate mechanism whereby hematopoietic lineage stem cell progeny could contribute to β-cell replication is by the generation of macrophages. In the macrophage-deficient colony stimulating factor 1 knock-out mouse (*op/op*), animals develop osteopetrosis as adults but young animals demonstrated abnormal islet morphogenesis, a much reduced β-cell mass and deficiencies in β-cell replication[61]. Islet neogenesis at the pancreatic ducts was enhanced, suggesting that islets could form but the β-cell population could not expand appropriately. There is also evidence that macrophages have a key role in islet angiogenesis through the expression of matrix metalloproteinase-9[62].

Most studies on the contribution of bone marrow-derived stem cells to β-cell survival or regeneration have transplanted cells with a genetic tag, such as green fluorescent protein, into irradiated recipient animals made diabetic with STZ or into diabetes-prone animals such as the NOD mouse[63,64]. As little as 1% allogeneic chimerism of repopulated marrow was able to reverse diabetes in the latter[64]. However, in human pancreata from individuals who had previously received hematopoietic stem cell transplants from the opposite gender, there was no evidence of colonization within the islets[65]. The mobilization of bone marrow stem cells to colonize the pancreas appears to be linked to the presence of pancreatic tissue damage in either the endocrine or exocrine compartments[62]. It cannot be assumed that the bone marrow-derived cells will be of equivalent lineage phenotype when they colonize the pancreas *vs* their subsequent ability to induce β-cell renewal. The entire environment of the pancreas following β-cell loss, including bone marrow-derived cells, the remodeled ECM and the cytokine/growth factor milieu, is likely to represent the combined elements necessary to optimize β-cell regeneration.

We utilized mice expressing Cre recombinase under control of the Vav promoter, which were crossed with ROSA26 yellow fluorescent protein (YFP) transgenic mice, such that hematopoietic lineage cells and their progeny could be tracked[66]. The Vav gene is ubiquitously but specifically expressed by all hematopoietic lineage cells where it functions as a signal transduction molecule and it remains active on differentiated cell progeny including T cells, B cells and macrophages[67]. YFP-tagged cells were

located within the pancreas at all ages, lining the ductal epithelium and around and within the islets. Following STZ treatment, the presence of these cells was significantly increased, temporally corresponding with a recovery of β-cell mass. No co-localization of insulin or other pancreatic endocrine hormones was found in the hematopoietic lineage cells but approximately 30% of such cells co-stained with CD31, a marker of macrophages, EPC and endothelial cells, which significantly increased after STZ. A sub-population of hematopoietic lineage cells around the islets demonstrated the macrophage markers F4-80 and Mac-1 and some large YFP-positive cells within the islets showed a nuclear presence of Pdx1 and could be endocrine progenitors. This strongly suggests that endogenous bone-marrow-derived stem cells are involved in β-cell recovery after induced diabetes.

EVIDENCE THAT EARLY NUTRITIONAL INSULTS IMPAIR β-CELL REGENERATION

Exposure to a LP diet during gestation affected pancreatic endocrine plasticity postnatally as mice were unable to recover β-cell mass following exposure to STZ[9]. In female animals, this was associated with a reduced number of islets relative to STZ treatment alone but this was not seen in males. Other studies have also shown that nutrient deficiency early in life affects tissue plasticity. A LP diet during gestation significantly impaired recovery of male adult rats following ischemia-reperfusion[68] while maternal calorie restriction during gestation and lactation impaired β-cell replacement after STZ treatment[69,70]. However, changes in islet morphometry resulting from prior exposure to dietary insult are not specific to β-cells, as the α-cell mass was also increased[9]. Thus, the change in islet tissue plasticity is likely to represent a fundamental change in phenotype in islet cell progenitors that contribute to multiple cell types. One type of progenitor that has been characterized in islet cells expresses the transcription factor Pdx1 but not insulin[38]. Such cells are rapidly able to differentiate into insulin-expressing β-cells *in vitro* and *in vivo* and may represent a strategic reserve of latent β-cells that could be mobilized in situations of extreme metabolic demand. We found that 4%-8% of islet cells in neonatal mice were Pdx1-positive but insulin-negative by immune-histochemistry[9]. Following exposure of mice to a LP diet during gestation, the offspring showed no change in the percentage of such cells that were present within islets. However, after exposure to STZ, the number of Pdx1-positive/insulin-negative cells was increased, which may indicate that normal maturational pathways that allow such cells to differentiate into functional β-cells are impaired following dietary insult.

Further evidence that dietary restriction in early life alters β-cell progenitor phenotype comes from manipulation of islets *in vitro*. We isolated islets from neonatal mouse islets previously exposed to a control diet or a LP diet fed to the mothers during gestation. Islets were de-differentiated by culture for 4 wk on a type 1 collagen matrix in the presence of epidermal growth factor to yield ductal epithelial cell-like monolayers[71]. The doubling time of cells from LP-fed offspring was significantly prolonged. Cell monolayers were then re-differentiated to form pseudo-islets over 4 wk by culture on Matrigel in the presence of insulin-like growth factor-Ⅱ (IGF-Ⅱ) and fibroblast growth factor-7. Cells derived from LP-fed mice demonstrated a relative impairment of pseudo-islet formation and insulin content and release. The relative gene expression of transcription factors involved in β-cell generation from precursors and endocrine hormones was determined by DNA microarray analysis. De-differentiated islet cultures showed a reduction in the expression of Pdx1, Pax6 and Ngn3, and of insulin and somatostatin mRNAs (Table 1). After pseudo-islets were subsequently generated, the expression of each of these genes returned to values close to those seen in fresh islets if the donor animals had been exposed to the control diet. However, in animals exposed to the LP diet, pseudo-islets did recover expression of transcription factors, insulin or somatostatin to a similar extent. These results suggest that a maternal LP diet alters pancreatic endocrine stem cell presence and phenotype in the offspring, leading to reduced islet plasticity in postnatal life, and that this can be demonstrated *in vitro*.

Table 1 Changes in relative gene expression assessed by DNA microarray for monolayer cells cultures

Gene	De-differentiate control diet	Re-differentiate control diet	Re-differentiate LP diet
Ins 1	-46.1	-0.1	-20.5
Somatostatin	-61.2	+2.0	-5.6
Pdx1	-1.7	-0.4	-2.3
Pax6	-23.0	-0.4	-15.7
Ngn3	-2.5	-0.5	-1.5

Values represent fold differences in mRNA expression relative to freshly isolated neonatal mouse islets (n = 3). Cell cultures were derived from the de-differentiation of neonatal mouse islets and subsequently re-differentiated to yield pseudo-islets. Donor animals were exposed to either control or low protein (LP) diet during gestation.

Maternal malnutrition can also alter the development of tissue vasculogenesis in the offspring, which may also limit β-cell plasticity through a disruption of endothelium-β-cell signaling. Offspring of pregnant rats given a LP diet during gestation exhibit a reduction in capillary density in a variety of tissues, including skeletal muscle, endometrium, ovaries and pancreatic islets[5,72-74]. Endothelial dilatation was similarly impaired[75]. Within the pancreas, the number of EPC, characterized as being nestin and CD34-positive, was significantly reduced in offspring of LP-fed mothers[6], which in other tissues has been associated with a reduced expression of IGF-Ⅱ[76].

REVERSAL STRATEGIES: ABILITY OF STATINS TO INCREASE β-CELL MASS

Statins are potent and safe drugs widely used to treat

familial dyslipidemia[77,78] and to lower cholesterol levels in patients with or at risk of cardiovascular disease[79]. However, statins also exert pleiotropic actions unrelated to their cholesterol-lowering effect. These include improvements in endothelial cell function such as increased NO synthesis and anti-oxidant effects[80], stabilization and reduction of atherosclerotic plaque[80-82] and inhibition of inflammatory responses as measured by circulating C-reactive protein and cytokines. In offspring of rats given a LP diet during gestation, blood vessel dilation was impaired but this was corrected by postnatal treatment with atorvastatin[83]. Diabetes is associated with a reduction in circulating EPC and their abundance in bone marrow[84]. This is likely be related to the increased presence of oxidized LDL-cholesterol which has been shown to decrease EPC migration, differentiation into endothelial cells and survival[85]. Statin treatment increased the mobilization of EPC from bone marrow in a diabetic pig model[86], increased proliferation of EPC *in vitro*[87] and delayed diabetes onset in two different mouse models of T1D, including STZ treatment[88]. This was independent of inhibition of HMG-CoA reductase activity[89].

Treatment of neonatal rats with atorvastatin significantly increased β-cell mass in both STZ-treated and control animals and improved glucose tolerance[90]. Atorvastatin treatment was associated with an increased number of intra-islet endothelial cells, suggesting that vasculogenesis had preceded the increase in β-cell mass. This was supported by an increase in the proportion of intra-islet endothelial cells undergoing DNA synthesis and a parallel increase in the proliferation rate of adjacent β-cells. Hyperglycemia induced apoptosis in isolated human pancreatic islet endothelial cells but this was prevented by exposure to statin *via* the Akt intra-cellular survival pathway[91]. It is not clear if the trophic effects of atorvastatin are exerted directly on the β-cells or if they are mediated by secondary trophic effects that enhance migration of bone marrow-derived stem cells into the pancreas and/or islet vasculogenesis.

What is the potential for using statins to increase the islet microvasculature and enhance β-cell mass in humans? In individuals with type 1 diabetes of duration greater than 10 years, treatment with atorvastatin for 6 mo in a placebo-controlled study resulted in a significant improvement in blood vessel flow-mediated dilation and C-reactive protein, a marker of inflammation[92]. Similarly, in young adults with type 1 diabetes with a mean age of 34 years and normal blood cholesterol, just 6 wk of treatment with atorvastatin resulted in improved flow-mediated dilation and reduced LDL-cholesterol[93]. Diabetic subjects with microalbuminurea similarly benefited from 6 wk of atorvastatin therapy with a significant decrease in apolipoprotein B, LDL-cholesterol and oxidized LDL[94]. Young, normo-cholesterolemic males with type 1 diabetes had endothelial dysfunction assessed by flow-mediated dilation which improved significantly after only 4 wk of treatment with pravastatin and reached control patient values[95]. These beneficial effects of statins on the vasculature of individuals with diabetes were demonstrated in the absence of hypercholesterolemia. Recently, a randomized, placebo-controlled clinical trial tested the effect of atorvastatin therapy over 18 mo on residual β-cell function in young adults with new onset type 1 diabetes[96]. C-peptide levels were measured after a mixed meal test as an indicator of endogenous insulin release. This gradually declined with time in both placebo and atorvastatin-treated subjects but was significantly better preserved with atorvastatin. This strongly suggests that statin treatment could help retain or enhance residual β-cell mass.

CONCLUSION

In summary, nutritional insults in early life result in decreased β-cell mass and function in the offspring that persists into adult life and provides increased risk of glucose intolerance and type 2 diabetes. This is likely to involve a restriction on β-cell plasticity that can be directly mediated through effects on β-cell progenitors and the function of mature β-cells, but may also be indirect through a decreased islet vasculogenesis and availability of EPC, resulting in an impaired trophic signaling between the vascular endothelium and the β-cell. Likely reversal strategies include the use of statins to improve microvascular volume and function.

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TOPIC HIGHLIGHT

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Mechanisms behind early life nutrition and adult disease outcome

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Abstract

Obesity is increasing around the globe. While adult lifestyle factors undoubtedly contribute to the incidence of obesity and its attendant disorders, mounting evidence suggests that programming of obesity may occur following under- and over-nutrition during development. As hypothalamic control of appetite and energy expenditure is set early in life and can be perturbed by certain exposures such as undernutrition and altered metabolic and hormonal signals, *in utero* exposure to altered maternal nutrition and inadequate nutrition during early postnatal life may contribute to programming of obesity in offspring. Data from animal studies indicate both intrauterine and postnatal environments are critical determinants of the development of pathways regulating energy homeostasis. This review summarizes recent evidence of the impact of maternal nutrition as well as postnatal nutrition of the offspring on subsequent obesity and disease risk of the offspring. While much of the experimental work reviewed here was conducted in the rodent, these observations provide useful insights into avenues for future research into developing preventive measures to curb the obesity epidemic.

Key words: Maternal obesity; Programming; Postnatal overnutrition; Postnatal undernutrition; Leptin; Neuropeptide Y

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INTRODUCTION

Obesity is a common disorder and an important risk factor for many chronic diseases. As the second biggest cause of mortality after smoking, obesity-associated complications account for 10% of health-care costs in most countries[1]. The prevalence of obesity, particularly childhood obesity, is rising worldwide. The reasons behind this epidemic are not clearly understood, however this metabolic disease can result from a complex interaction between many factors including genetic, physiological, behavioural and environmental influences. The rate at which this disease has increased suggests that environmental and behavioural factors such as increased consumption of high-fat and high-energy foods, coupled with reduced physical activity play a greater role than genetic causes[2-4]. It is therefore particularly relevant that recent epidemiological and animal studies have suggested that long-term health can be influenced by events in fetal

and early infant phases of life. Nutritional status during "critical windows" in early development is thought to influence or "program", the onset of major diseases in adulthood[5] (Figure 1). The mechanisms underlying this development of obesity and associated disease in adulthood are not yet completely understood. This review will discuss the effects of nutritional imbalances *in utero* and in early postnatal life as well as the mechanisms that may contribute to the development of adult disease.

FETAL ORIGINS OF DISEASE

One of the first studies to highlight the fetal origins of disease was a population study in Hertfordshire demonstrating a link between low birth weight and weight at 1 year of age and increased death rate from ischemic heart disease, impaired glucose tolerance and type 2 diabetes[6,7]. This led to the "Thrifty Phenotype" hypothesis, where poor nutrition *in utero* led to fetal adaptations that produced permanent changes in insulin and glucose metabolism, increasing the risk of developing the metabolic syndrome in adulthood[8]. A more recent hypothesis is the "Predictive Adaptive Response" hypothesis[9], which proposes that the fetus makes adaptations *in utero* or during the early postnatal developmental period based on the predicted postnatal environment. When the predictive adaptive response is appropriate the phenotype is normal, however when the predicted and actual environments do not match, disease manifests[9]. Epidemiological data indicate that maternal obesity is linked to offspring obesity, and a child's body mass index (BMI) correlates with that of the mother[10]. Thus both undernutrition, and maternal obesity have been shown to increase the risk of obesity in offspring. In support of these hypotheses, a large number of studies have been carried out, where maternal nutrition has been altered during gestation and early postnatal life.

METABOLIC PROGRAMMING IN UTERO

In determining the mechanisms involved in metabolic programming, the use of animal models has been paramount. A benefit of using non-human species is the capacity to rigorously control diet and other relevant environmental factors that impact on obesity. In altricial species such as rat the lactation period correlates with the third trimester of human gestation. Initial animal experiments examining early life programming influences on subsequent obesity risk dealt with the impact of undernutrition during gestatsaion, utilizing restricted feeding, uterine ligation or protein deprivation of the mother. The effects of maternal undernutrition, low protein diets and nutritional excess have diverse effects on the offspring, as recently reviewed[11-13].

MATERNAL UNDERNUTRITION

Maternal protein restriction during gestation has previously been shown to result in low birth weight of the offspring and impaired development of organs such as the pancreas and kidney[14] leading to impaired glucose tolerance and insulin resistance in peripheral tissues. There is also strong evidence that these animals will develop obesity later on in life[15]. In a rat model of total caloric restriction during pregnancy, offspring are hyperphagic, hyperinsulinemic and develop obesity and hypertension[16]. Other models of early growth restriction have produced similar findings, together with an amplification of the metabolic disturbances when a highly-palatable or high-fat diet is introduced postnatally[16-18].

MATERNAL OVERNUTRITION

Rodent models of maternal overnutrition usually involve the feeding of a high fat diet to pregnant dams, resulting in the development of a phenotype comparable to that of the human metabolic syndrome[11]. Offspring have altered neuron development[19,20], increased adiposity and blood pressure, impaired cardiovascular function[21], and become hyperinsulinemic and hyperglycemic in adulthood[22]. More recent studies have shown that offspring from obesity-prone rats developed adiposity and impaired glucose and lipid metabolism as early as postnatal day 20[23,24] and this was maintained until adulthood[25]. Furthermore, maternal high fat diet during the preconceptional period and/or throughout pregnancy and lactation has also been shown to result in a similar obesity phenotype in the offspring independent of postnatal nutrition[26]. These recent studies highlight the profound impact that dietary interventions during pregnancy could have on the long-term health of the offspring.

METABOLIC PROGRAMMING IN THE POSTNATAL PERIOD

Maternal diet during the suckling period is also important as several regulatory mechanisms not fully developed at birth undergo significant maturation in the early postnatal period. This is more marked in rodents, as they undergo rapid maturation of most organ systems after birth. The important influence of the suckling period is supported by rodent studies where reducing rat litter sizes to 3-4 pups from 10-12 pups per dam, increases milk availability resulting in offspring with dyslipidemia, hyperinsulinemia, hyperleptinemia, increased body weight and fat pad mass[27-34]. This model was designed by McCance who demonstrated that the adjustment of rat pup litter size during lactation changes the milk intake of the pups and this resulted in a lifetime of programming of the growth trajectory[35]. A subsequent study added to these initial observations suggesting that the amount of food consumed in early life plays an important role in determining the pattern of food intake in later life[36]. To further support the importance of the postnatal period, a recent epidemiological study demonstrated that rapid weight gain in neonatal life is associated with increased risk of obesity in later life, independent of birth weight and

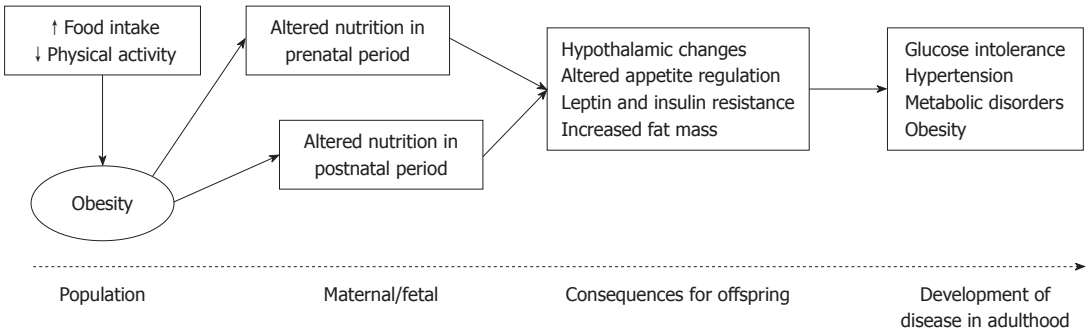

Figure 1 Obesity is increasing at the population level, in part due to increased energy intake and reduced energy expenditure, contributing to increasing pre-pregnancy body mass index. Overnutrition during gestation and early development is thought to influence or "program" appetite and metabolic regulation, which in turn affects the risk of major disease in adulthood.

weight at 1 year of age[37]. Thus, rapid weight gain mainly results from neonatal overfeeding, highlighting the importance of this period of development in programming of adult disease. Although a recent study demonstrated that maternal obesity exerted a stronger detrimental impact on the offspring phenotype compared to overnutrition during the early postnatal period, pre- and postnatal nutritional excess were shown to interact with each other to exert additive detrimental effects on programming of central appetite regulators and glucose and lipid metabolism[24,38].

MECHANISMS MEDIATING THE DEVELOPMENTAL PROGRAMMING OF DISEASE

There are a growing number of signals and pathways that have been shown to be involved in energy homeostasis, some of which are listed in Table 1. Alteration of one or more relevant pathways during early development plays a major role in the programming of obesity and associated adulthood diseases. These mechanistic pathways can be located both centrally and peripherally.

Central mechanisms

Alteration in the environment during a "critical period" of development may alter the normal development of the neuronal circulatory regulating food intake. Recent evidence shows that there are physiological differences in the regulation of energy balance between adults and neonates. Although much is known about the neurocircuitry in adults, the development of important appetite regulating systems such as the neuropeptide Y (NPY) and melanocortin systems remains unclear.

The ontogeny of the NPY system has been extensively studied by Grove and associates. Initial studies demonstrated that NPY was not only abundantly expressed in the arcuate nucleus (ARC) but transient expression of NPY was also observed in the other hypothalamic regions, including the dorsomedial hypothalamus, paraventricular nucleus, lateral hypothalamus and the perifornical region which is not evident in adulthood[39]. NPY levels in all areas were low at postnatal day 2 (P2), increased rapidly to peak at P15-16 and returned to levels observed in adulthood in the ARC, while in the other areas NPY was no longer apparent after P30[39].

Table 1 Central and peripheral signals involved in the control of energy homeostasis

Orexigenic	Anorexigenic
Peripheral	
Adipose tissue:	Adipose tissue:
Adipsin	Leptin
Glucocortiocoids	Adiponectin
Angiotensin Ⅱ	Resistin
	Tumour necrosis factor α
Stomach:	Gut:
Ghrelin	Cholecystokinin
	Peptide YY
	Obestatin
	Pancreas:
	Insulin
	Amylin
	Pancreatic polypeptide
Central	
Neuropeptide Y	α-melanocyte stimulating hormone
Agouti related peptide	Cocaine and amphetamine regulated transcript
Melanin concentrating hormone	Corticotrophin releasing hormone
Orexin A and B	Urocortin
Galanin	Serotonin
Noradrenaline	Dopamine
Cannabinoid	

The development of important neuronal circuits regulating appetite occurs late in gestation and continues postnatally in rodents, suggesting that the normal development of this system may be susceptible to environmental and nutritional changes after birth. A series of early studies demonstrated that the amount of food consumed during suckling in the rat plays an important role in determining food intake later in life[36]. This may contribute to long-term development of Syndrome X-like alterations, such as insulin resistance, obesity and increased blood pressure[30]. Recent data extends these observations, demonstrating that maternal consumption of "junk" food during gestation and lactation led to increased preference for "junk" food in offspring as they matured[40].

Peripheral mechanisms

Leptin and insulin signaling appears to be important for the development of the appetite regulating system. In the rodent during the first 3 wk of life, leptin is unable to alter feeding or energy expenditure[41]. During the neonatal period a surge of leptin is evident, which does not correlate with body fat[42]. In rodents, fetal adipocytes and placenta produce very low levels of leptin late in gestation[43], so the main source for this surge of leptin may be the transplacental transfer of maternal leptin to the fetus[44]. This neonatal hyperleptinemia however, is not able to affect growth, food intake or energy expenditure in mice and rats as the neuronal circuits are still not developed[32,45]. Recently it has been suggested that this leptin surge is actually an important signal for the initiation of the development of ARC projections in the rodent[46]. The main evidence for this is the incomplete development of ARC projections in *ob/ob* and *db/db* mice that do not have a functioning leptin system[47]. On the other hand, exogenous leptin treatment during the early postnatal period in rodents can also cause abnormal expression of NPY, agouti-related peptide and pro-opiomelanocortin in the ARC[45], however the effect on the projections is unknown. Hyperleptinemia caused by overfeeding during this period can also cause abnormalities in hypothalamic circuits[48,49]. Collectively these findings suggest that a certain level of leptin is required during the "critical period" of development and both deficiency and excess can have long-term detrimental effects on the hypothalamic circuitry that regulates energy homeostasis.

Insulin receptors are also highly expressed in the fetal brain of rodents and humans, with expression declining during the postnatal period[50]. Insulin treatment during the postnatal period results in increased body weight, chronic hyperinsulinemia and increased blood pressure that persists into adulthood[51], suggesting abnormal insulin levels during a "critical period" of development may cause long-term defects in the regulation of energy homeostasis[49]. Insulin may also be an important trophic factor, however more studies are needed to determine its role in the development of the feeding circuits.

Adipose tissue development can also be affected during the fetal and postnatal periods. Development of adipose tissue commences *in utero*, where adipocytes have the ability to develop into either brown or white adipose tissue (WAT)[52]. The main function of brown adipose tissue (BAT) is to convert energy into heat[53], whereas the WAT represents an endogenous energy store that is capable of secreting a number of mediators involved in the regulation of energy metabolism, neuroendocrine function and immune function[54].

BAT is present in rodents throughout life but until recently it was thought that BAT in humans was only present in early life and did not have any important function in adults[53]. The presence of BAT in rodents has been shown to be important in body weight and energy regulation as well as glucose metabolism[53,55] while active BAT in adult humans has been demonstrated following cold exposure[56]. A recent study was able to demonstrate a functioning BAT in adult humans, particularly females, using combined positron-emission tomography and computed tomography scanning[57]. Furthermore, the same study demonstrated an inverse correlation between the amount of BAT and BMI[57]. The ability to measure and locate the mass and activity of BAT will help to better understand the physiological role of BAT in adult humans and its potential as a therapeutic target in the management of obesity[57].

Over the last decade WAT has become recognized as an important endocrine organ able to secrete a vast number of hormones as well as expressing numerous receptors that allow it to respond to traditional hormone systems as well as signals from the central nervous system[54,58]. The wide range of protein signals and factors that have been identified in WAT highlights the complexity of this system which is highly integrated into the general homeostatic mechanisms of mammals[59]. WAT development is characterized by a rapid increase in fat cell number until 4 wk of age, followed by slower rate of growth until puberty, whereas increase in adipose tissue mass during maturity is mainly due to increased adipocyte size[60]. The increase in fat mass during early life appears to be dependent on an increase in local glucocorticoid action during the postnatal period[61]. The ability of glucocorticoids to promote lipogenesis and decrease lipolysis[62], highlights their role as important mediators in the development of central obesity, which can contribute to hypertension and glucose intolerance[63]. Corticosterone production driven by the enzyme 11β-HSD1 could play a pivotal role in the growth and development of the adipose tissue[64]. Further evidence of programming of the adipose tissue was recently provided by a study, which showed that increased maternal nutrition in the sheep led to upregulation of peroxisome proliferator activated receptor γ, lipoprotein lipase and leptin in fetal tissue, thereby predisposing the offspring to enhanced adipose accumulation[65].

PERSPECTIVES

Evidence from both epidemiological and animal studies suggests that the programming of obesity and adulthood disease arises from multifactorial influences occurring early in life. Adipocyte development, leptin, insulin and glucocorticoid signaling, as well as the plasticity of the hypothalamus all play a major role in the programming of appetite and metabolism, possibly leading to development of associated diseases. While the intrauterine environment and early postnatal window are critical determinants, recent data from our laboratory highlighting the detrimental impact of paternal high fat diet-induced obesity on offspring glucose tolerance and pancreatic β cell function, highlights the possibility that unhealthy paternal diets can reprogram gene expression in offspring, implicating epigenetics in these trans-generational effects[66].

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Munich, Germany

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Sydney, NSW, Australia

February 16-19, 2011
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London, United Kingdom

February 24-26, 2011
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Buenos Aires, Brazil

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British Columbia, Canada

February 28-March 1, 2011
Childhood & Adolescent Obesity: A Whole-system Strategic Approach
Abu Dhabi, United Arab Emirates

March 3-5, 2011
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Gainesville, FL, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011, Birmingham
England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology
Jacksonville, FL , United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey
March 28–30, 2011
The Second World Congress on Interventional Therapies for Type 2 Diabetes
New York, United States

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Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
Chicago, IL, United States

June 2-5, 2011
The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

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Stockholm, Sweden

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INSTRUCTIONS TO AUTHORS

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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Patent (list all authors)

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Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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