Fetal and Neonatal Programming on Postnatal Growth and Feed Efficiency in Swine

胎猪和新生仔猪程序化对出生后生长和饲料利用率的影响

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I. INTRODUCTION

引言

Pork Meat and Pig Production
猪肉和猪的生产

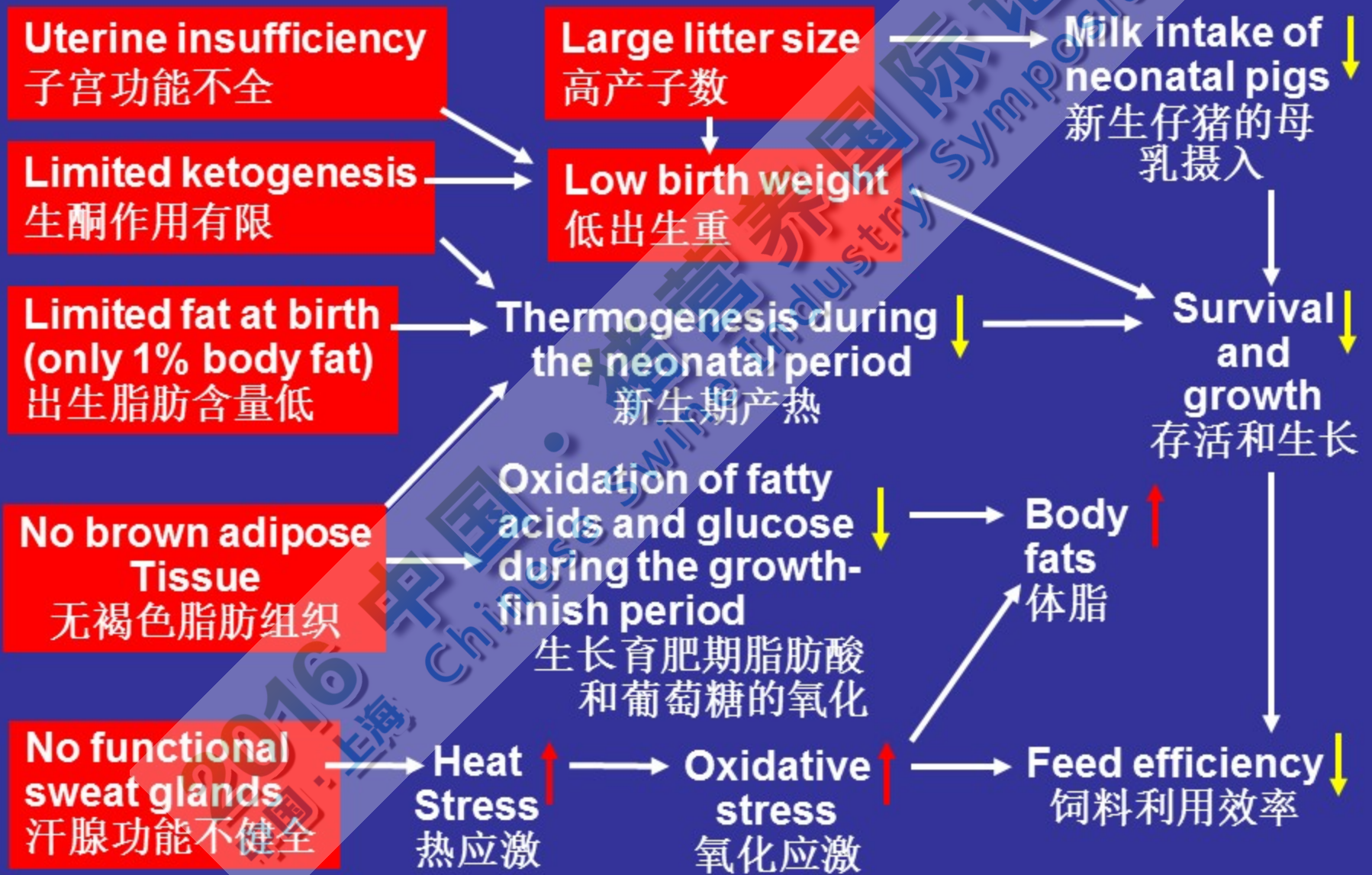
Pork provides high-quality protein for human consumption. Pork meat is the most important source of animal protein in China and many other nations.
猪肉为人类提供高品质的蛋白。猪肉是中国和许多其他国家最为重要的动物蛋白来源。

However, in terms of nutrition and management, it is the most challenging to raise pigs among livestock animals.
但是，猪的饲养在营养和管理方面，面临着比其它家畜更大的挑战。

This is because of the unique characteristics of swine biology.
这是由于猪在生物学上的特性。

Wu et al. Ann. N.Y. Acad. Sci. 2014;1328:18-28

Unique Biology of Swine
猪的生物学特性



II. REGULATION OF FETAL GROWTH AND DEVELOPMENT

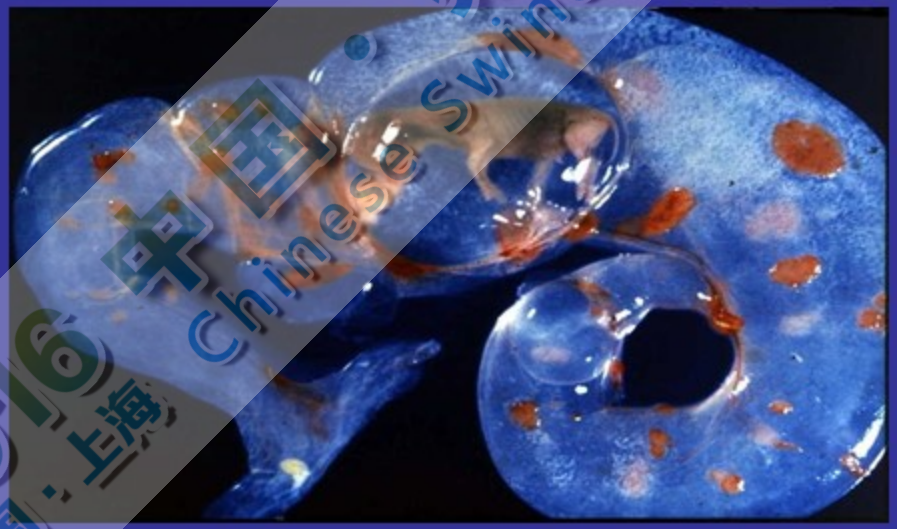
胎儿生长和发育的调控

--- Fetal growth and development is regulated by *genetics, epigenetics, maternal maturity, and environmental factors (e.g., nutrition).*

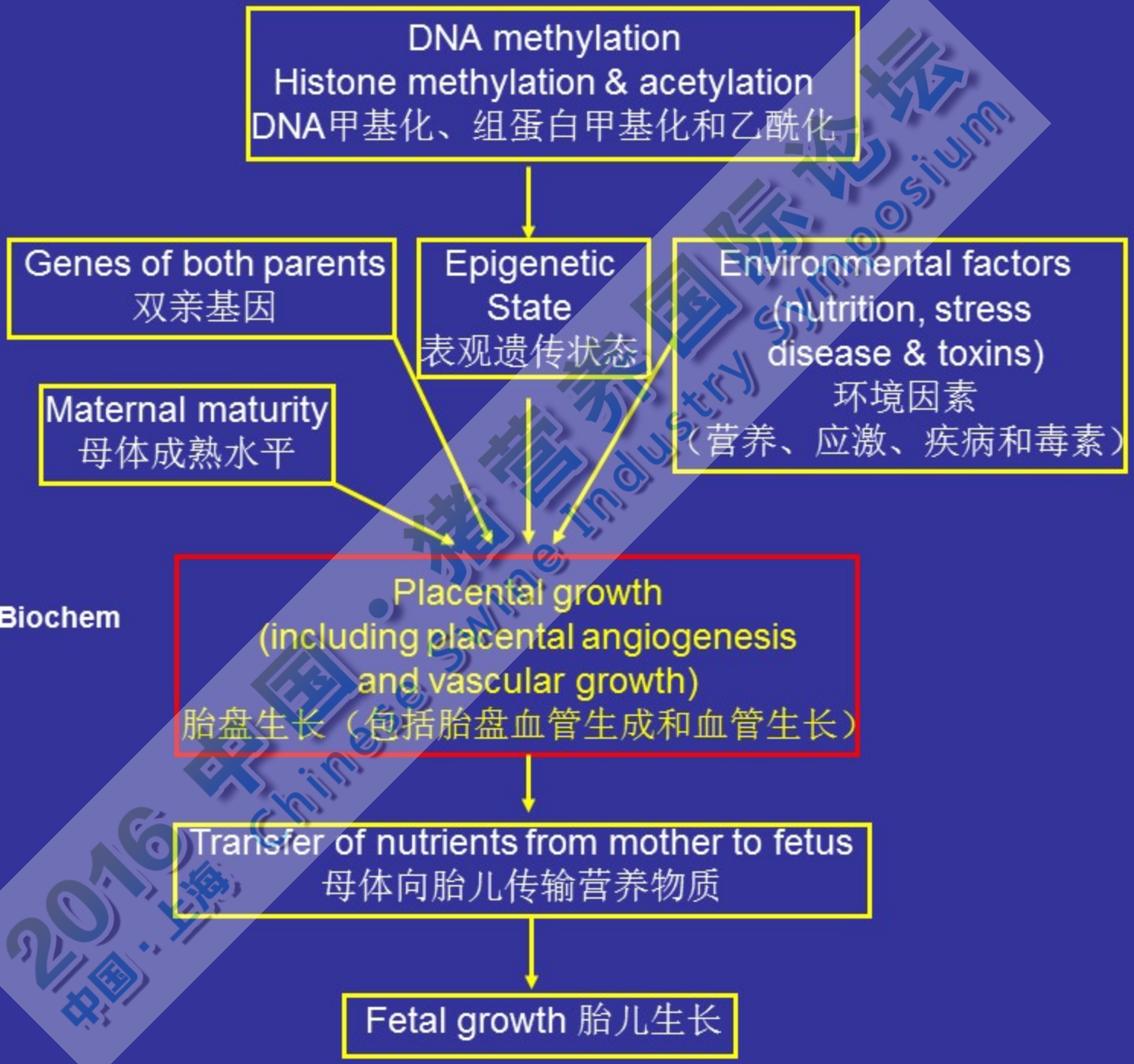
胎儿生长和发育是由基因学、表观遗传学、母体成熟水平和环境因素调控。

--- IUGR is defined as impaired growth and development of the mammalian embryo/fetus or its organs during pregnancy. (< 1.1 kg birth weight)

IUGR被定义为哺乳动物胚胎/胎儿或者其器官在妊娠期生长和发育损伤。(< 1.1 kg出生重)



Wu et al. J Anim Sci 84: 2316-2337, 2006



Ji et al. J Nutr Biochem 2016; 27:1-8

IUGR in Swine
猪的宫内生长受限

Naturally occurring IUGR
(e.g., litter-bearing animals)
自然发生的IUGR（例如多胎动物）

Environmentally-induced IUGR
(e.g., over- and undernutrition, heat stress, disease, and toxins)
环境诱导的IUGR（例如营养过剩或不足、热应激、疾病和毒素）

Production-imposed uterine insufficiency
(e.g., increased litter size through breeding or reproductive technologies and early breeding at 70-80% of mature BW)

生产技术提高导致的子宫功能不全（例如通过育种和繁殖技术提高产子数，以及在后备母猪达到成熟体重的70-80%时实施早期繁育技术）

Foxcroft et al. J Anim Sci. 2006;84:E105-12.

Uterine Insufficiency and IUGR
子宫功能不全和IUGR

When an embryo is transferred from a genetically larger mother to a recipient dam with a lower uterine capacity.
当胚胎从遗传表型大子宫容量的母体移植到一个小子宫容量的母体会导致IUGR。

When an embryo is transferred from a genetically smaller mother to a recipient dam with a higher uterine capacity.
当胚胎从基因表型小子宫容量的母体转移到大子宫容量的母体可以促进胎儿生长。

Freking et al. Anim Reprod Sci. 2016;167:16-21

Experimentally-Induced Undernutrition
试验诱导的营养不良

Well-controlled experimental studies have demonstrated that maternal undernutrition during the peri-breeding or gestation period reduces fetal growth in pigs.

试验研究表明，在围产期和怀孕期，母猪营养不良将导致胎猪的生长受限

Undernutrition → IUGR

营养不良

Prenatal growth of all species is sensitive to maternal nutrition at *all stages* between oocyte maturation and birth.

在卵母细胞成熟到胎儿出生的任何阶段，所有物种的胎盘生长都容易受到母体营养的影响

Atinmo et al. J Anim Sci. 1974;39:703–11;
Bazer et al. Reproduction 2009;138:195–209

Overnutrition and IUGR
营养过剩和IUGR

Increasing energy and protein intake during a short period of time (termed "flushing") around conception can increase the number of embryos/fetuses, but often results in increased porcine embryo and fetal mortality.

在配种前短期内提高母猪的能量和蛋白摄入（即催情补饲）能够增加胚胎/胎儿数量的阶段，但往往会导致母猪胚胎和胎儿死亡率的提高。

Obese Sow
肥胖母猪

IUGR
pigs
IUGR仔猪

Overfeeding is a waste of feed and does not increase porcine litter size at birth.

过量饲喂既会浪费饲料，也不能增加母猪的产子数。

Ashworth CJ. Anim Reprod Sci. 1991;26:311–21

Overnutrition and IUGR
营养过剩和IUGR

Overfeeding during all or part of the gestation also has a detrimental effect on pregnancy outcomes in pigs.

在母猪怀孕的整个或者部分阶段，营养过剩也会对妊娠结局造成有害的影响。

Overnutrition → IUGR

营养过剩

Bazer et al. J Anim Sci. 1968;27:1021–6;
Cole. J Reprod Fertil Suppl. 1990;40:67–82;
Einarsson and Rojkittikhun. J Reprod Fertil Suppl. 1993;48:229–39;
Nelson and Robison. J Anim Sci. 1976;43:71-7

High Intake of Dietary Protein Reduces Litter Size in Gilts
高日粮蛋白摄入降低后备母猪产子数

Variable 变量	Dietary crude protein (%) 日粮粗蛋白				
	10	12	14	16	Pooled SEM
Maternal plasma ammonia (μM) 母体血氨	56^{d}	70^{c}	81^{b}	93^{a}	1.7
Total number of piglets born alive per litter 出生活仔数/母猪	9.62^{bc}	9.95^{a}	9.74^{b}	9.48^{c}	0.07
Total number of piglets weaned at d 21 per litter 21天活仔数/母猪	8.46^{b}	9.04^{a}	8.76^{b}	8.53^{c}	0.05

There were 30 gilts in each treatment group. 每个处理30头母猪。
a-d: $P < 0.05$.

III. IMPLICATIONS OF IUGR FOR ANIMAL GROWTH AND FEED EFFICIENCY

IUGR对动物生长和饲料利用效率的影响

Organ Dysfunction and Abnormal Development
器官功能紊乱和发育不良

Testes 睾丸
Ovaries 卵巢
Brain 大脑
Heart 心脏
Skeletal muscle 骨骼肌
Liver 肝脏
Thymus 胸腺
Small intestine 小肠
Wool follicles 毛囊
Mammary gland 乳腺

IUGR → **Multiple Systems**
多系统

McMillen IC and Robinson JS. Physiol Rev 85: 571-633, 2005;
Reynolds et al. Mol Cell Endocrinol. 2012;354:54-9;
Wu et al. J Nutr. 2004;134:2169-2172

Reductions of Muscle and Intestine in IUGR Pigs
IUGR降低仔猪肌肉和肠道重量

Newborn pigs 新生仔猪	Tissue weight at birth (g) 组织出生重	
	Small intestine 小肠	Skeletal muscle[1] 骨骼肌
Normal birth weight (1.43 kg) 正常体重	45.5 ± 1.5	23.3 ± 0.8
Low birth weight (0.86 kg) 低出生重	23.5 ± 0.5*	11.2 ± 0.4*

Data are means ± SEM, n = 8. 数据=平均数 ± SEM。

[1] Gastrocnemius muscle. 腓肠肌。

* P < 0.01.

Wang et al. J Nutr. 2008; 138:60-66.

Reductions of Glutathione in Muscle and Intestine in IUGR Pigs (0.86 kg) vs Normal Pigs (1.43 kg)

IUGR降低仔猪肌肉和肠道内谷胱氨肽含量（0.86 kg vs 1.43kg)

Newborn pigs 新生仔猪	GSH (μmol/g tissue)	GSSG (nmol/g tissue)	GSSG/GSH (μmol/μmol)
	Small intestine 小肠		
Normal birth weight 正常出生重	2.74 ± 0.16	129 ± 4.5	0.046 ± 0.002
Low birth weight 低出生重	2.06 ± 0.11*	150 ± 4.8*	0.072 ± 0.003*
	Skeletal muscle[1]骨骼肌		
Normal birth weight 正常出生重	1.10 ± 0.05	53 ± 1.7	0.048 ± 0.003
Low birth weight 低出生重	0.84 ± 0.04*	65 ± 2.2*	0.077 ± 0.004*

Data are means ± SEM, n = 8. 数据=平均值± SEM。

[1] Gastrocnemius muscle. 腓肠肌。

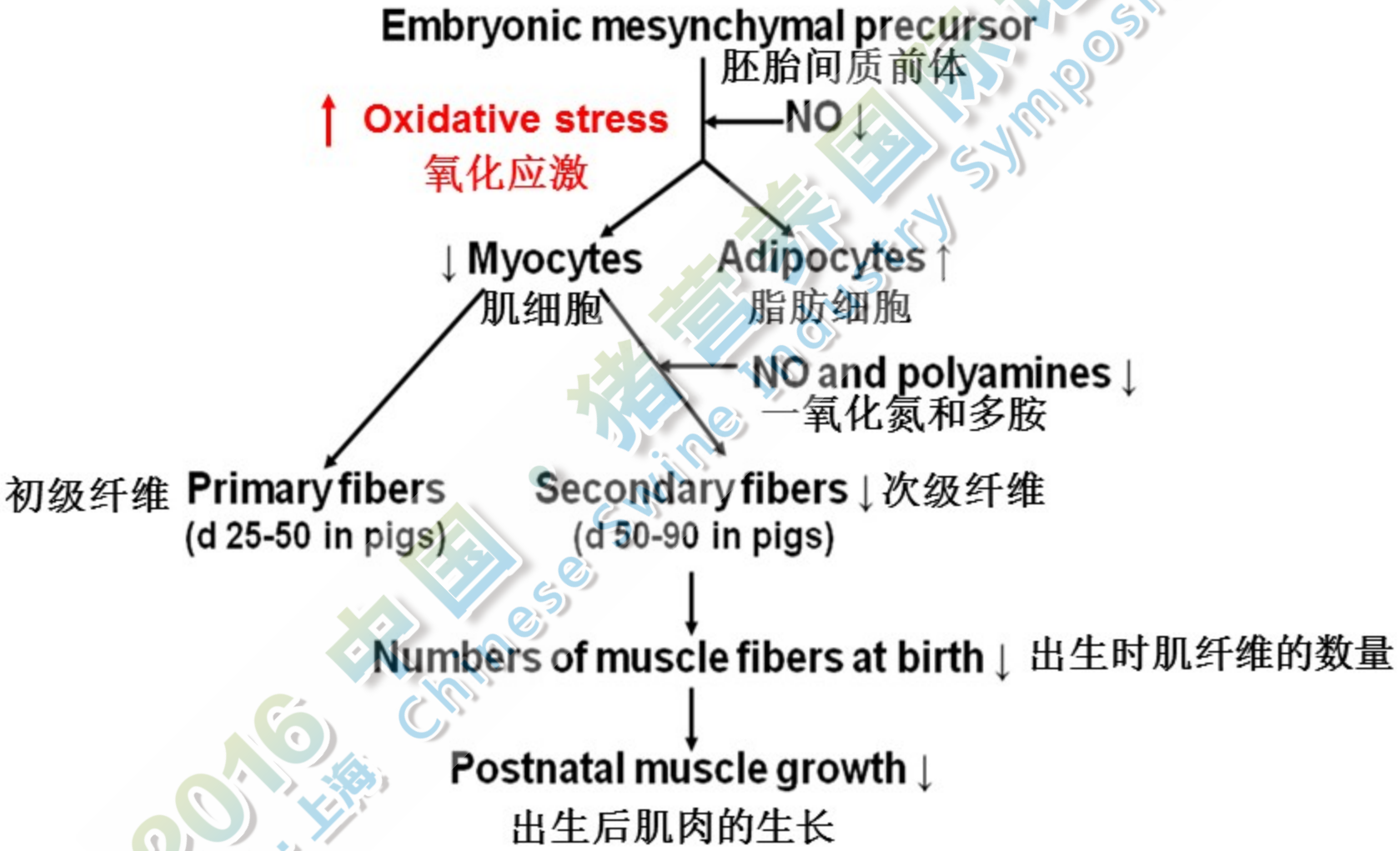
GSH = Glutathione (reduced form) 还原型谷胱氨肽

GSSG = Oxidized glutathione 氧化型谷胱甘肽

GSSG/GSH = Indicator of oxidative stress 氧化应激指标

Development of fetal muscle fiber is impaired in IUGR pigs

IUGR仔猪在胎儿期肌肉纤维发育受损



Wu et al. J Anim Sci. 2010;88:E195-E204

***Body and tissue composition* 机体和组织组成**

↑ **Whole-body and intramuscular fat mass (+ 1% to 10%)**
全身和肌肉内脂肪含量（增加1%-10%）

↑ **Connective tissue content**
结缔组织含量

↓ **Skeletal muscle fiber number (- 10% to 20%)**
骨骼肌纤维数量（降低10%-20%）

↓ **Meat quality**
肉品质

***Cardiovascular disorders* 心血管紊乱**

↑ **Coronary heart disease**
冠心病

↑ **Hypertension**
高血压

↓ **Endothelial function**
内皮功能

Oksbjerg et al. J Anim Sci. 2013;91:1443-53;
Rehfeldt et al. Domest Anim Endocrinol. 2004;27:267-85
Wu et al. J Anim Sci 84: 2316-2337, 2006.

Postnatal Growth 出生后的生长

--- No change in feed intake per kg body weight.
每公斤体重采食量没有变化。

↓ Whole-body and skeletal muscle growth (- 5% to 10%)
全身和骨骼肌的生长（降低5%-10%）

↓ Efficiency of feed efficiency (weight gain/feed intake) (- 5% to 10%)
饲料利用效率（降低5%-10%）

↓ Skeletal system development
骨骼系统发育

Hormonal imbalance 激素水平紊乱

↑ Plasma levels of glucocorticoids and renin
血浆糖皮质激素和肾素水平

↓ Plasma levels of thyroid hormones & anabolic hormones
血浆甲状腺激素和同化激素水平

(e.g., insulin, growth hormone, and IGF-I) (- 15 to 30%)
(如胰岛素，生长激素和胰岛素样生长因子) （降低15-30%）

Schinckel et al. Prof Anim Scient. 2010;26:51-69;
Schoknecht et al. Pediatr Res. 1997;42):201-7.

Reductions of Feed Efficiency in Growing IUGR Pigs
IUGR降低仔猪生长期饲料利用效率

Body weight (kg) 体重	Difference in gain:feed ratio between IUGR pigs (1-kg birth weight) and large-birth weight pigs (2-kg birth weight) IUGR仔猪（体重1kg）和大出生重仔猪（体重2kg）料重比的差异
47	10.0% ↓
65	8.0% ↓
84	5.1% ↓
103	4.8% ↓

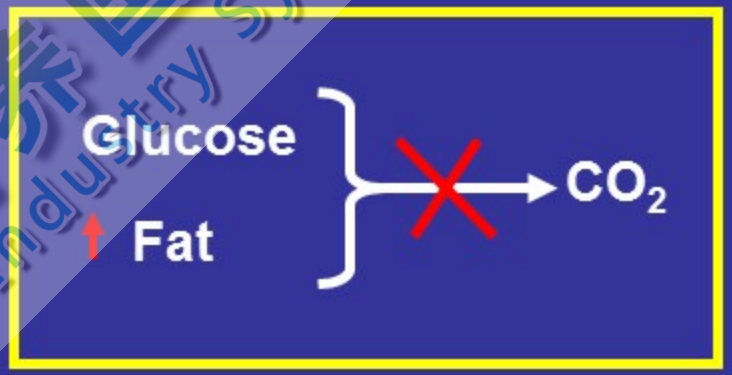
Gilts with 1-kg birth weight require 13 more days to reach 125-kg birth weight than gilts with 2-kg birth weight.

出生重1公斤的后备母猪要比出生重2公斤的母猪多饲养>13天才能达到125公斤体重

Powell and Aberle. J Anim Sci. 1980;50:860–8;
Schinckel et al. Prof Anim Scient. 2010;26:51-69

Metabolic disorders 代谢紊乱

Insulin resistance
胰岛素抵抗
β-Cell dysfunction
β细胞功能紊乱
Dyslipidemia
血脂异常
Glucose intolerance
葡萄糖不耐症
Impaired energy homeostasis
能量稳态受损
Obesity肥胖
Type-II diabetes II型糖尿病
Oxidative stress 氧化应激
Mitochondrial dysfunction 线粒体功能障碍



Barker and Clark. Rev Reprod 2: 105-112, 1997.
Wang et al. Antioxid Redox Signal. 2012;17:282-301

Neonatal Mortality, Health and Adjustment
新生儿的死亡率、健康和适应性

↑ **Stillbirths** ***(IUGR is responsible for most of stillbirths in animals.) (+ 20% to 50%)***
死胎（IUGR是动物死胎的主要原因）（提高20%-50%）

↑ **Morbidity and mortality** ***(In livestock, most IUGR neonates die in the first wk of life.) (7- to 10-fold)***
发病率和死亡率（在家畜中，大多数IUGR新生儿在出生后第一周死亡。）（提高7-10倍）

↓ **Adjustment to the extrauterine life (e.g., behavior and suckling)**
出生后的适应能力（例如，行为和吮吸）

McMillen IC and Robinson JS. Physiol Rev 85: 571-633, 2005;
Reynolds et al. Mol Cell Endocrinol. 2012;354:54-9;
Wu et al. J Nutr. 2004;134:2169-2172

Transgenerational Effects of Fetal Nutrition
胎儿营养的跨代遗传效应

Compared to female pigs with a normal birth weight, IUGR pigs exhibit:
与正常体重母猪相比IUGR母猪表现为：

(1) Delay or failure to express estrus, conceive or farrow;
延迟或者不能发情、受孕或者产子
(2) Reduced preweaning and postweaning growth performance in affected offspring; and
降低受影响后代的断奶前后的生长性能
(3) Such adverse effects of IUGR can be carried for up to five generations.
IUGR引起的这些负面作用能够持续长达五代。

Freking et al. Anim Reprod Sci. 2016;167:16-21

IV. MECHANISMS OF FETAL PROGRAMMING

胎儿程序化的机制

Fetal and Neonatal Programming
胎儿和新生儿程序化

The intrauterine environment of the conceptus (e.g., *fetal nutrition* and endocrine status) may alter expression of the fetal genome and have life-long consequences. This phenomenon is termed "*fetal programming*".

孕体的子宫内环境（如胎儿营养和内分泌状态）可能改变胎儿基因组的表达，并产生终生的影响。这种现象被称为“胎儿程序化”。

Structure
结构
Endocrine
内分泌
Metabolism
代谢
Physiology
生理

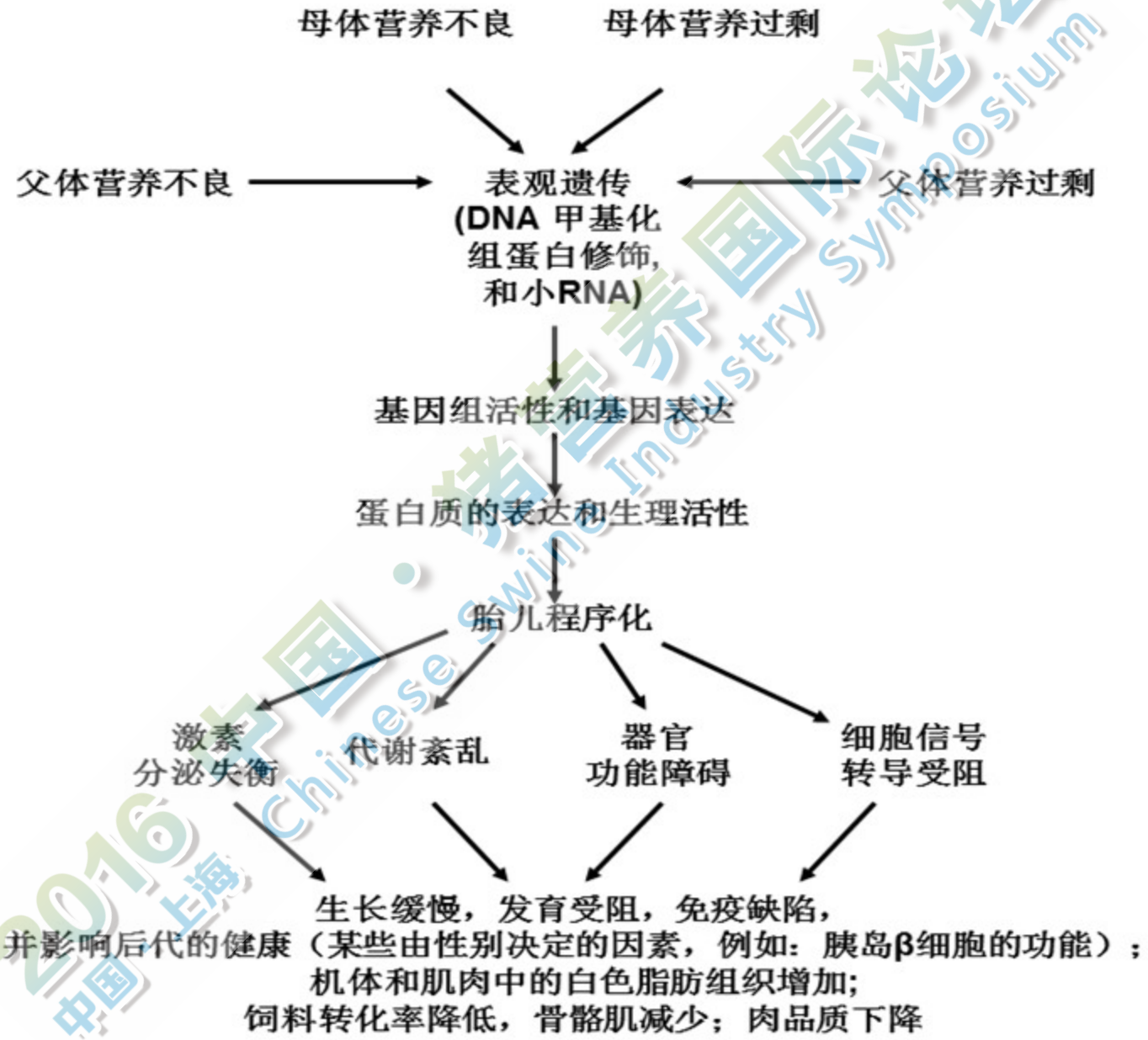
Growth *生长*
Development *发育*
Health *健康*
Disease *疾病*

Häfner SJ. Biomed J. 2016;39:166-76.

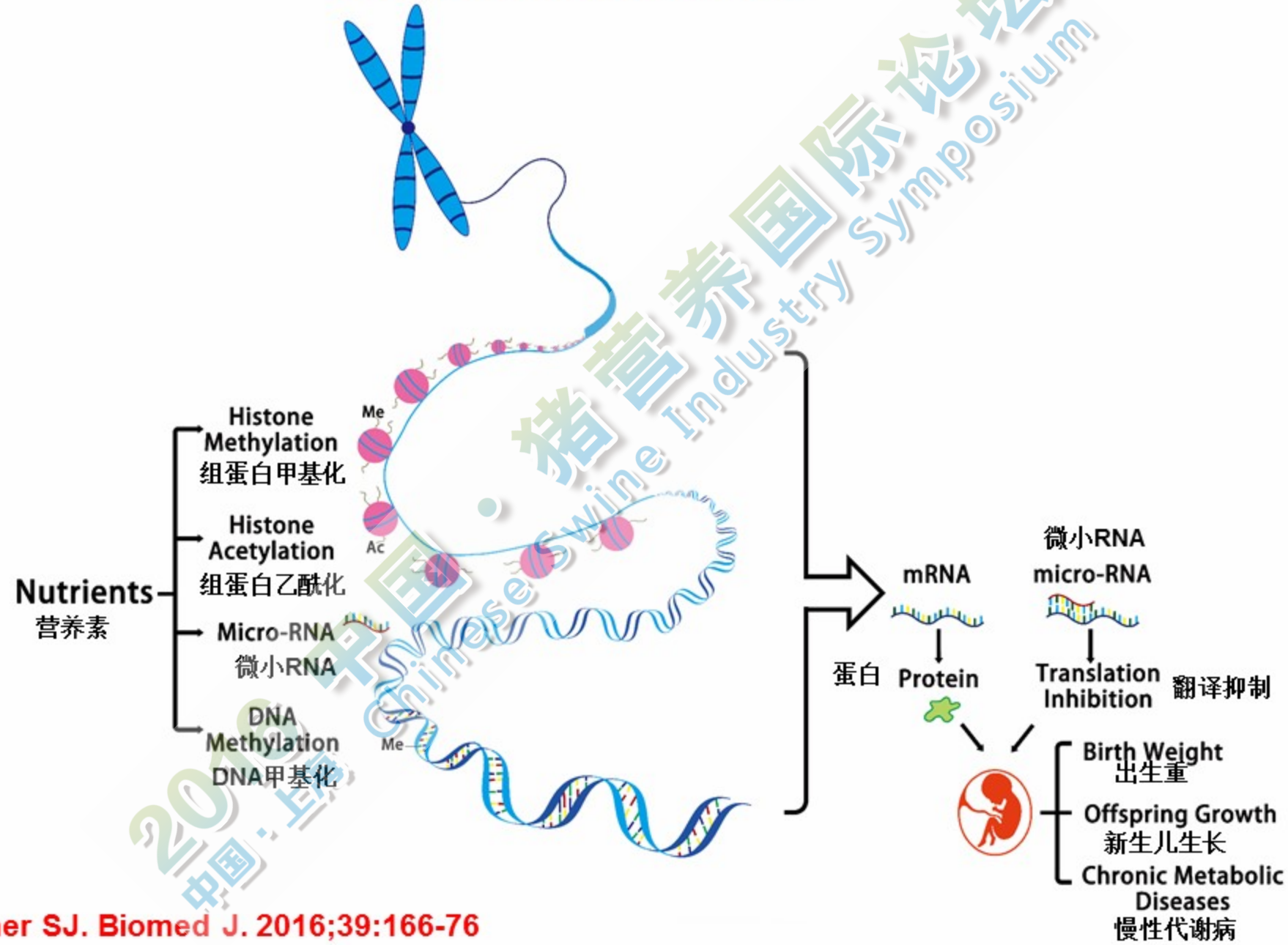
Fetal and Neonatal Programming

胎儿和新生儿程序化

Ji et al. J Nutr Biochem 2016; 27:1-8



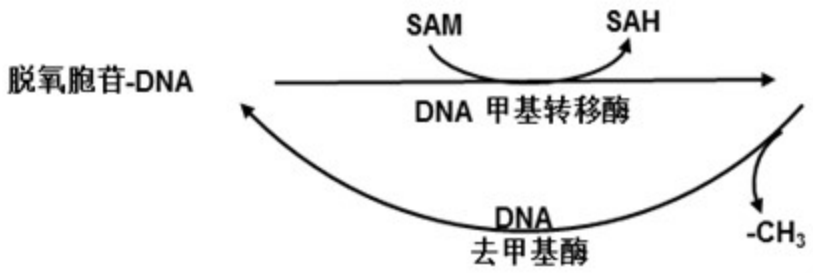
Epigenetic Regulation of Gene Expression
基因表达的表观遗传学调控



Häfner SJ. Biomed J. 2016;39:166-76

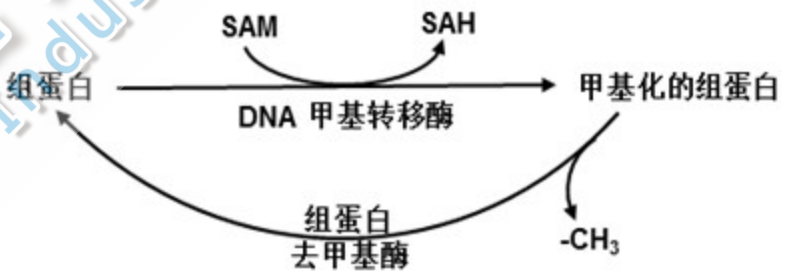
Fetal and Neonatal Programming
胎儿和新生儿程序化

1. DNA 甲基化

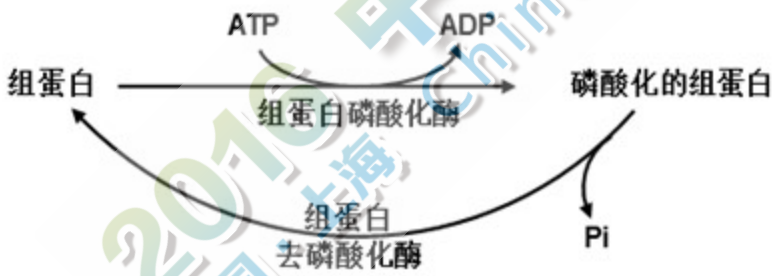


2. 组蛋白乙酰化

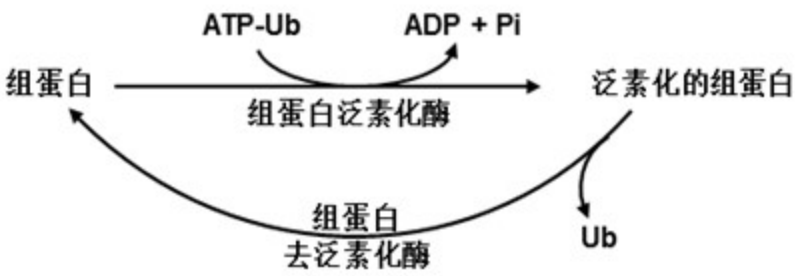
3. 组蛋白甲基化



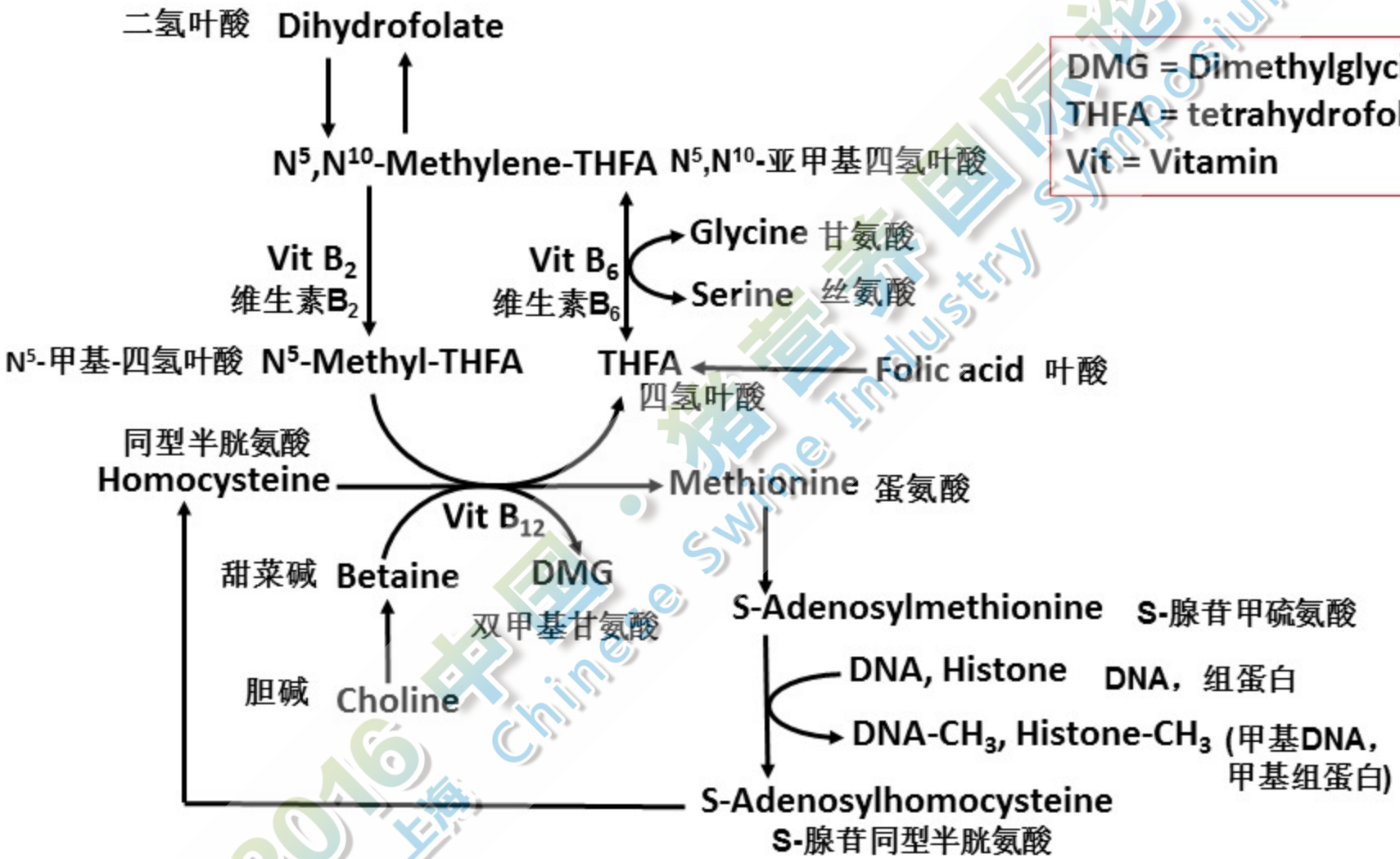
4. 组蛋白磷酸化



5. 组蛋白泛素化

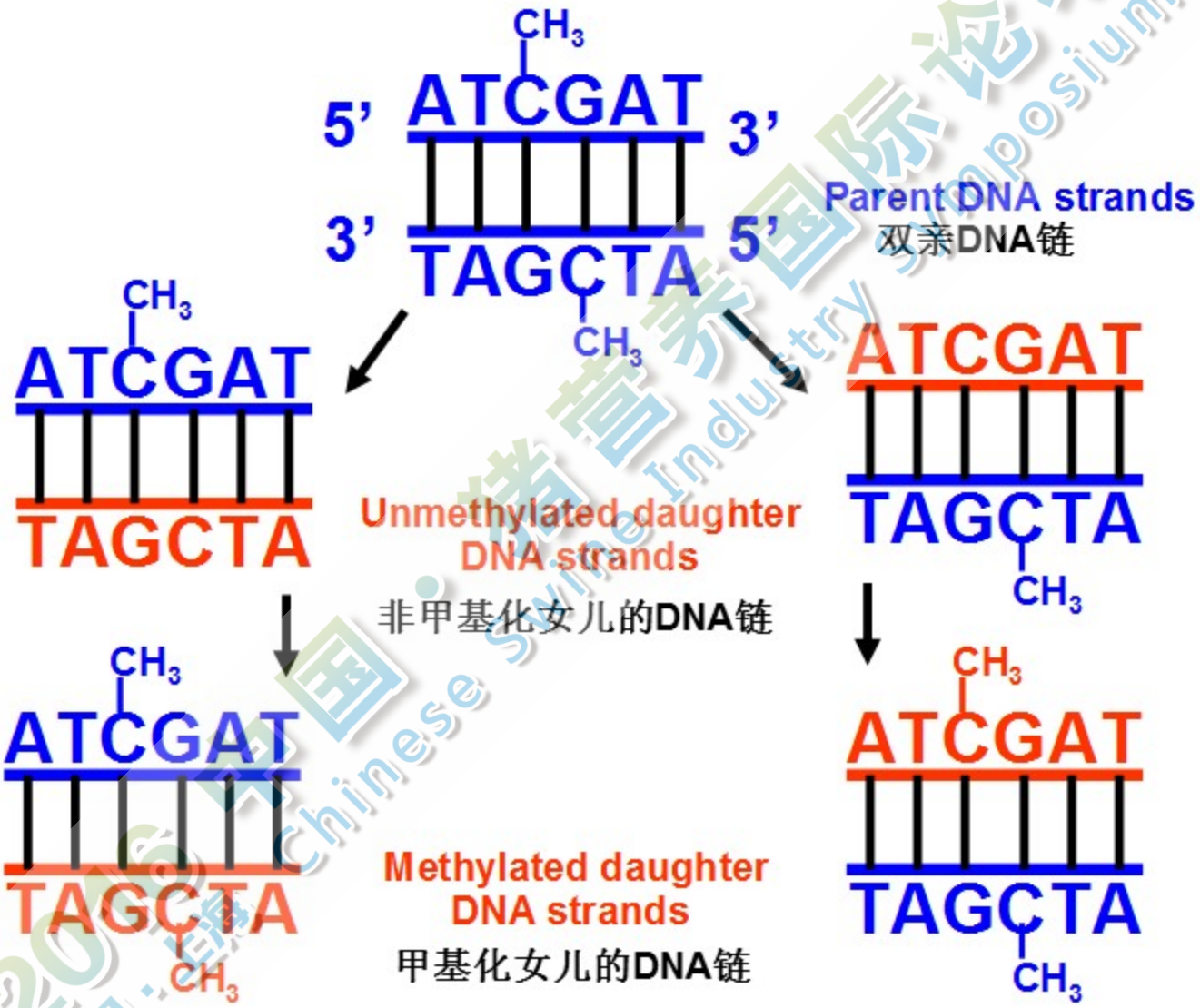


Major Donors of Methyl Groups for DNA and Protein Methylation
DNA和蛋白甲基化的主要甲基基团供体



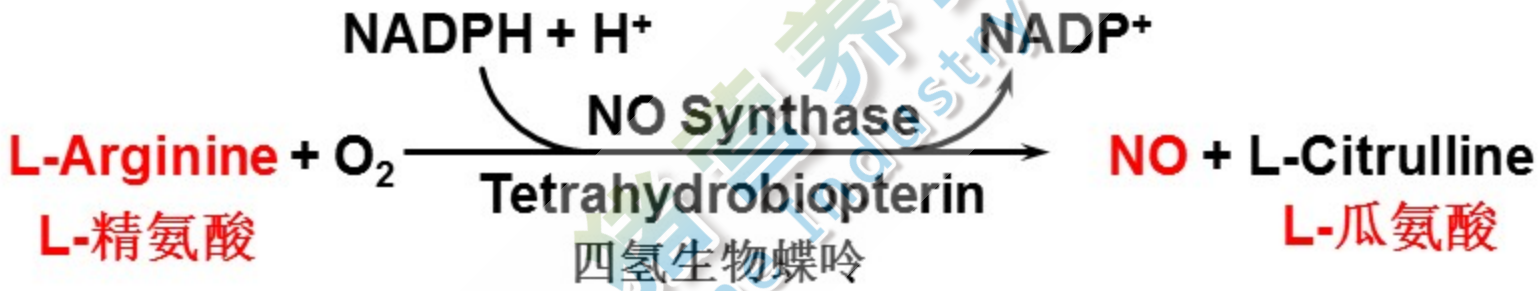
Brosnan et al. Biochem J. 2015;472:135-46

DNA Methylation Explains Transgenerational Effects of Nutrition
DNA甲基化诠释营养的跨代遗传效应



IUGR Reduces Expression of Many Genes in the Porcine Placenta and Fetus, Including Nitric Oxide (NO) Synthase

IUGR降低母猪胎盘和胎儿的许多基因的表达，包括一氧化氮合成酶



Wu et al. (2008) Amino Acids 2008; 35:691-702

Placental Growth and Uteroplacental Blood Flows
胎盘生长和子宫胎盘血流

The *placenta* is the organ that transports nutrients, respiratory gases, and the products of metabolism between maternal and fetal circulation.
胎盘是母体与胎儿之间运输营养物质、呼吸气体，以及代谢产物的器官。

***Placental growth (including vascular growth)* is crucial for fetal growth and development.**
胎盘生长（包括血管生长）对于胎儿生长和发育至关重要。

Reynolds et al. J Physiol 572: 51-58, 2006.

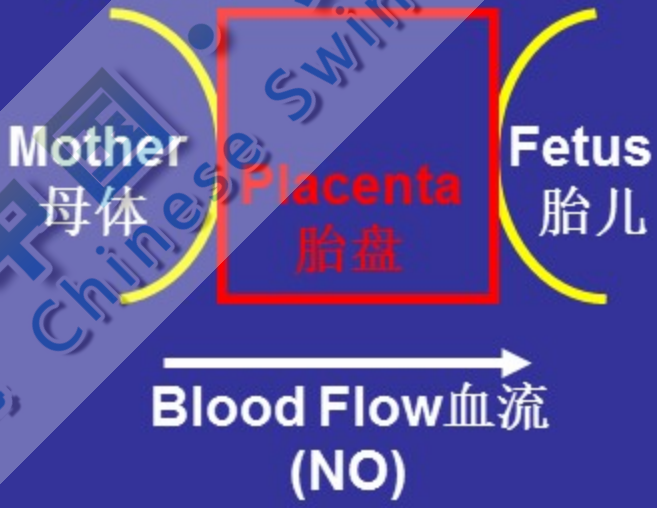
Rates of uteroplacental blood flows depend on placental vascular growth, which results from ***angiogenesis*** (the growth of new vessels from existing ones) and ***placental vascularization***.

子宫胎盘血流的速率取决于胎盘血管的生长，而胎盘血管生长是血管生成（基于已有血管的新血管的生长）和胎盘血管化的结果。

Placental growth
胎盘生长

Placental vascularization
胎盘血管形成

→ **Uteroplacental blood flows**
子宫血流

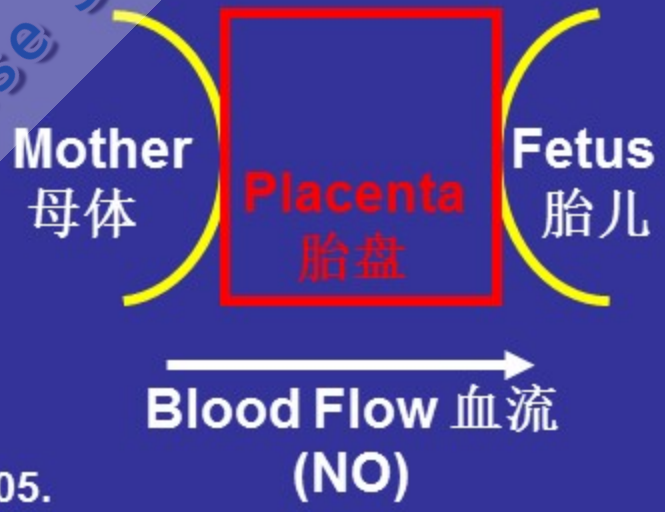


Reynolds et al. J Physiol 572: 51-58, 2006.

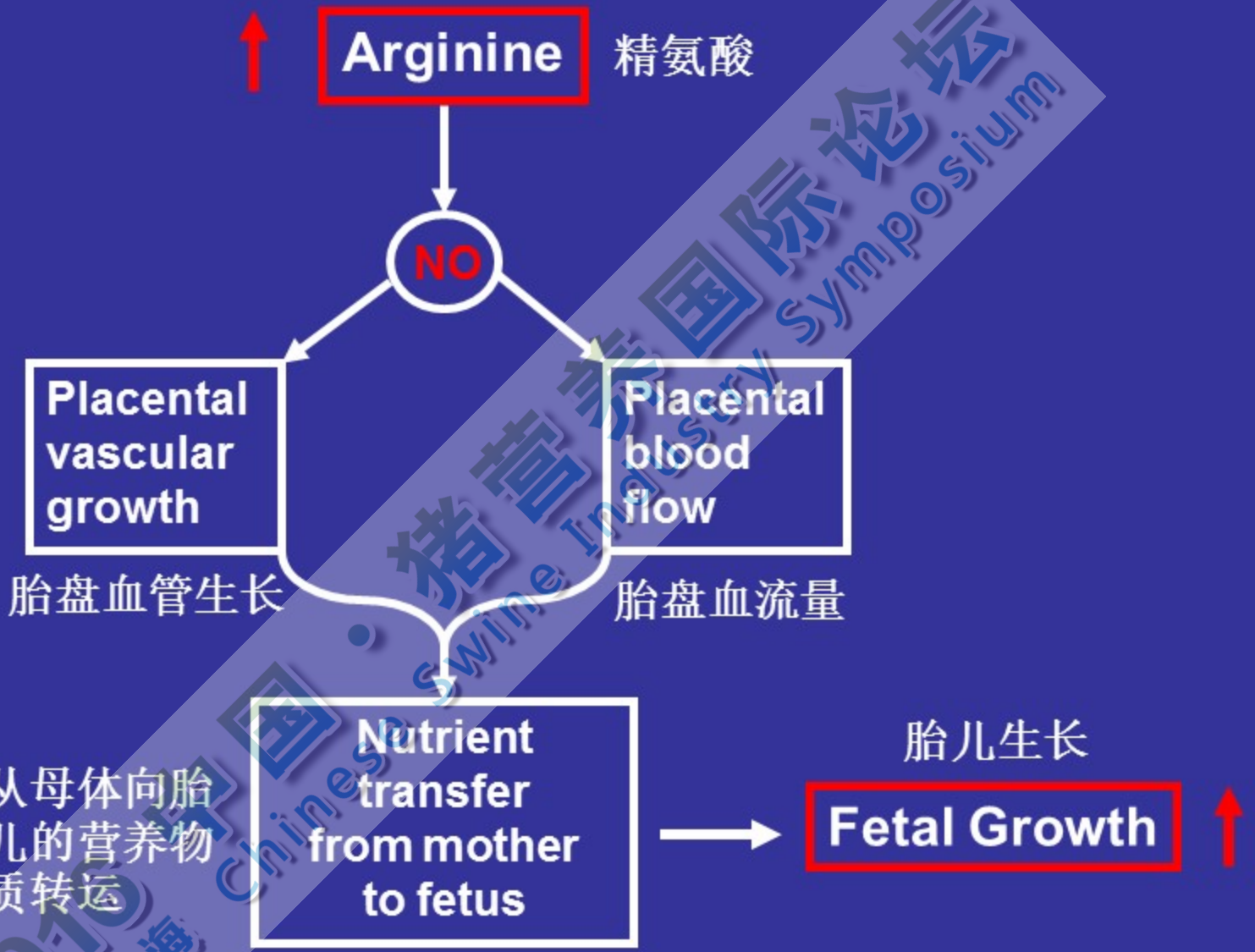
Impaired Placental Blood Flow in IUGR
IUGR损伤胎盘血流

Insufficient **uteroplacental blood flows and reduced transport activity in natural uterine insufficiency.**
自然情况下子宫功能不全表现为子宫胎盘血流量低和转运活性降低

Both *undernutrition* of adult ewes and *overnutrition* of adolescent ewes during pregnancy reduced placental proliferation and placental expression of angiogenic factors.
怀孕期间成年母羊的营养不足和青壮年母羊的营养过剩都会降低胎盘细胞增殖和胎盘血管生成因子的表达。



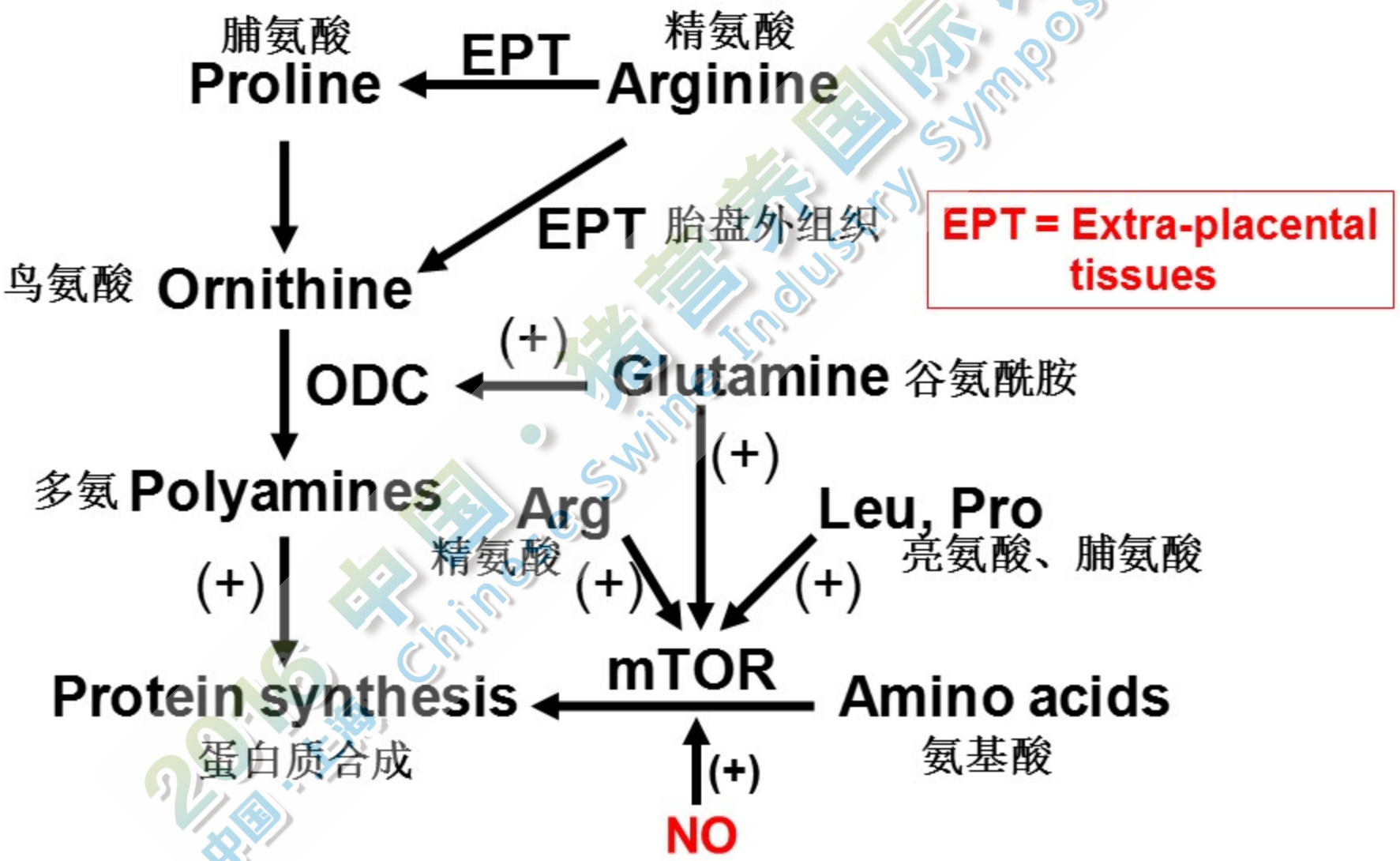
Wallace at al. *J Physiol* 565: 19-26, 2005.



Wu et al. J Nutr 134: 2169-2172, 2004.

Arginine, Glutamine and Proline Enhance Protein Synthesis in the Porcine Conceptus

精氨酸、谷氨酰胺和脯氨酸提高猪孕体的蛋白合成

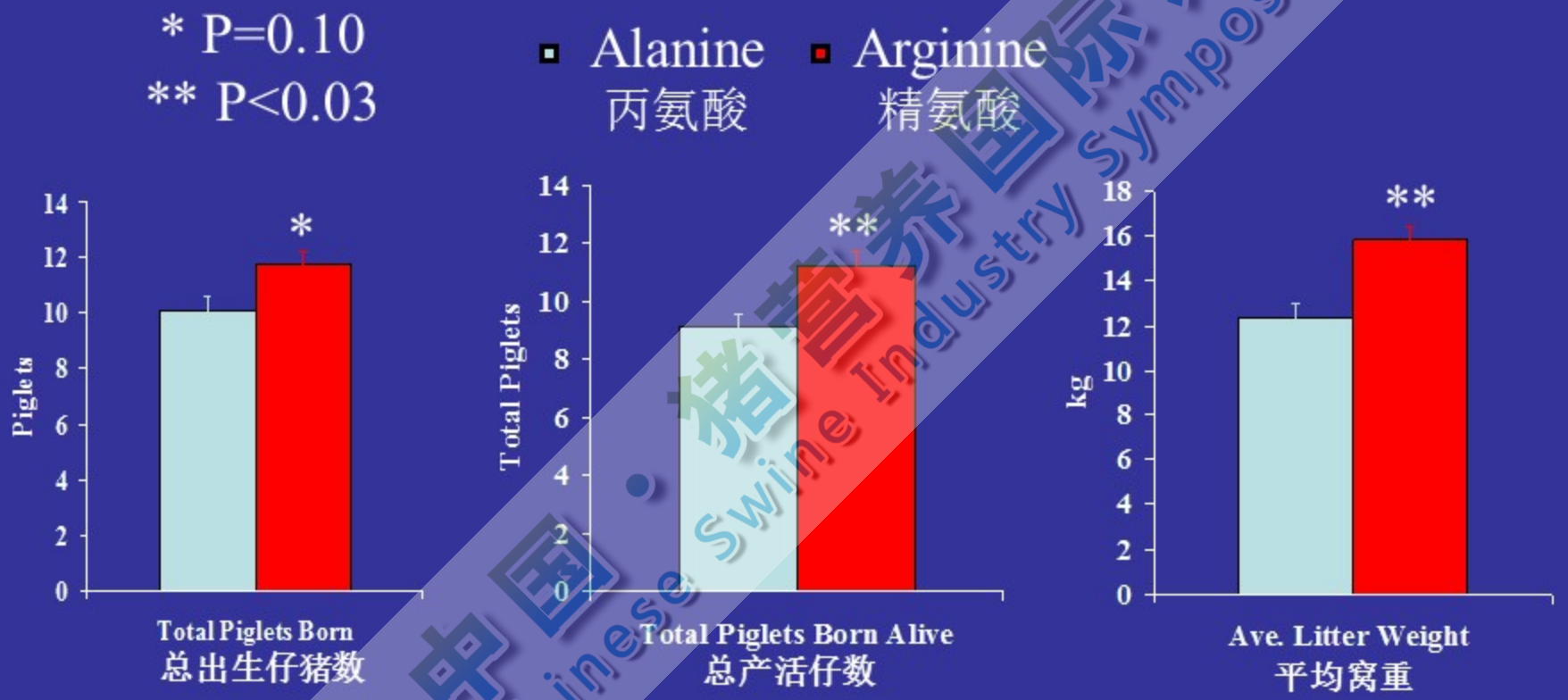


Wang XQ et al. (2016) Biol Reprod

V. MECHANISMS-BASED SOLUTIONS TO ENHANCING PIG GROWTH AND FEED EFFICIENCY

提高猪生长和饲料利用率的机制化解决措施

Dietary L-Arginine Supplementation Enhanced Fetal Growth in Pigs
日粮添加L-精氨酸提高胎猪的生长



Gilts (n = 53) were fed a corn- and soybean meal-based diet supplemented with 1% L-arginine-HCl or isonitrogenous L-alanine between Days 30 and 114 of gestation.
在妊娠30-114天，后备母猪饲喂玉米-大豆基础日粮，其中添加1%的L-精氨酸盐酸盐或者等氮量的丙氨酸（n=53）

Mateo et al. (2007) J. Nutr. 137: 652-656.

Dietary supplementation with arginine (Arg) increases the volume of fetal fluids and conceptus survival and growth in gilts (Days 14 – 25 of gestation).

日粮添加精氨酸增加后备母猪（处于14-25天妊娠期）胎液量、孕体的成活率和生长。

Variable 变量	Control	0.4% Arg	0.8% Arg
Number of gilts (n) 后备母猪数	14	15	14
Live fetuses (n) 活胎	10.5^{b}	12.7^{a}	12.2^{a}
Embryonic mortality (%) 胚胎死亡率	24.7^{a}	11.2^{b}	10.1^{b}
Total placental weight (g) 总胎盘重量	93^{b}	125^{a}	113^{a}
Total amniotic fluid (mL) 总羊水体积	2.52^{b}	4.06^{a}	3.42^{a}

a-b: $P < 0.05$

Li et al (2014) Amino Acids 46:375-384

Worldwide Studies that Reported Beneficial Effects of Dietary Arginine Supplementation on Embryonic and Fetal Survival in Gestating Sows

饲料添加精氨酸对妊娠母猪胚胎和胎儿生存率产生有利作用在世界范围内的报道

澳大利亚	Australia (De Blasio et al. 2009):	1% Arg (d 17-33)
中国	China (Gao et al. 2012):	0.8% Arg (d 22-114)
荷兰	The Netherlands (Ramaekers et al. 2006):	1% Arg (d 14-28)
新西兰	New Zealand (Campbell 2009):	1% Arg (d 14-28)
瑞典	Sweden (Bérard and Bee 2010):	1% Arg (d 14-28)
美国	United States (Li et al):	0.8% Arg (d 14-28)

Wu et al. (2013) Amino Acids 45:241-256

Reproductive performance of gilts fed diets supplemented with or without 1% glutamine (d 30 – 114 of gestation)
日粮添加或不添加1%谷氨酰胺对后备母猪（妊娠30-114天）繁殖性能的影响

Variable 变量	Control	Glutamine
Total piglets born alive per litter, n 每窝出生仔猪存活总数	10.2 ± 0.70	10.4 ± 0.65
Average birth wt of all piglets born alive, kg 所有存活仔猪平均出生体重	1.33 ± 0.04	1.41 ± 0.03*
Total litter wt at birth for all live piglets, kg 所有存活仔猪的出生总窝重	13.7 ± 0.75	14.7 ± 0.59*
Variation in birth wt among all piglets born, % 所有仔猪间出生体重的差异	16.4 ± 0.9	11.0 ± 0.6*
Variation in birth wt among live-born piglets, % 存活仔猪间出生体重的差异	14.3 ± 0.7	10.6 ± 0.5*
% of IUGR piglets at birth (< 1.1 kg BW) 出生仔猪患IUGR的比例	24.8	15.2**
Preweaning mortality for all live-born piglets, % 所有出生存活仔猪断奶前的死亡率	11.3	6.1**

Wu et al. (2011) J Anim Sci 89:2017-2030

Reproductive performance of gilts fed diets supplemented with or without two functional amino acids (Arg + Gln)[a]

日粮添加或者不添加两种功能性氨基酸（精氨酸+谷氨酰胺）对后备母猪繁殖性能的影响

Variable 变量	Control (n=32)	Arg+Gln (n=30)	Pooled SEM
Total piglets born per litter, 每窝仔猪出生总数	11.03	11.90 *	0.40
Total piglets born alive per litter, 每窝仔猪存活总数	9.91	11.33*	0.33
Total litter wt at birth for all piglets born, kg 每窝出生仔猪总重	14.6	16.0 *	0.36
Total litter wt at birth for all live piglets, kg 每窝存活仔猪总重	13.4	15.4 *	0.32
Piglets born dead per litter, 每窝仔猪出生死亡数	1.13	0.57 *	0.12
Variation in birth weights among all piglets born alive, % 所有存活仔猪间出生体重的差异	15.1	11.5 *	0.53

[a] 0.4% arginine + 0.6% glutamine (d 30 - 114)

Wu et al. (2010) J Anim Sci 88: E195-E204

CONCLUSION 结论

Fetal growth is controlled by *complex interactions* among genetic, epigenetic, and environmental factors, as well as maternal maturity.
胎儿的生长受到基因、表观遗传、环境因素以及母体成熟度等因素的复杂交互作用的调控。

These factors regulate *placental growth* (including placental angiogenesis and vascular growth) and, therefore, utero-placental blood flows and the *transfer of nutrients* from mother to fetus.
这些因素可调控胎盘的生长（包括胎盘血管生成和血管生长）、子宫-胎盘血流量以及营养素从母体向胎儿的转移）

IUGR results from *disturbances* of these maternal and fetal homeostatic mechanisms. It has important implications for pig growth and feed efficiency.
这些母体与胎儿间平衡机制的紊乱会导致IUGR的产生。这对猪的生长与饲料效率有着重大的影响。

Improving amino acid and vitamin nutrition may provide an effective means to prevent and treat adverse impacts of fetal and neonatal programming in swine. 改善母猪氨基酸和维生素营养，是防止和解决胎儿及新生仔猪程序化造成的不良影响的有效方法。

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