33ª REUNIÃO CBNA - AVES, SUÍNOS E BOVINOS

Nutrigenômica na vaca de corte gestante

Miguel Henrique de Almeida Santana

11/11/2021

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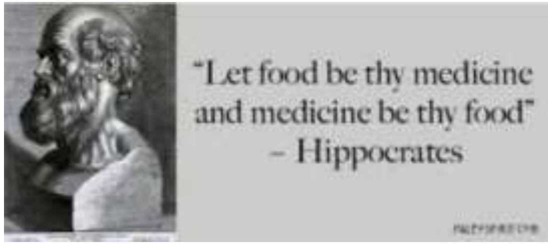
GENÔMICA NUTRICIONAL

Histórico

- 400 a.C.: Hipócrates especula a hipótese que o calor corporal é inato
- 400 a.C.: Hipócrates indica a alimentação como cura
- Século XIX: Liebig identifica carboidratos, proteínas, lipídeos e outros macronutrientes liberam calor
- Séculos XVIII e XIX: Era da nutrição química e analítica



Histórico

- Século XX: era biológica de estudos em metabolismo e química dos alimentos
- Século XXI: era pós-genômica
- Após Projeto Genoma Humano: evolução da bioinformática permitindo os avanços nas ciências ômicas

Genômica nutricional

- Sequenciamento dos genomas foi um marco na pesquisa de diversas áreas
- Em 1999 surgiu o termo Genômica Nutricional
- Relação da nutrição com a genética

Science AAAS

Nutritional Genomics: Manipulating Plant Micronutrients to Improve Human Health
Dean DellaPenna, *et al.*
Science **285**, 375 (1999);
DOI: 10.1126/science.285.5426.375

REVIEW

Nutritional Genomics: Manipulating Plant Micronutrients to Improve Human Health

Dean DellaPenna

The nutritional health and well-being of humans are entirely dependent on plant foods either directly or indirectly when plants are consumed by animals. Plant foods provide almost all essential vitamins and minerals and a number of other health-promoting phytochemicals. Because micronutrient concentrations are often low in staple crops, research is under way to understand and manipulate synthesis of micronutrients in order to improve crop nutritional quality. Genome sequencing projects are providing novel approaches for identifying plant biosynthetic genes of nutritional importance. The term "nutritional genomics" is used to describe work at the interface of plant biochemistry, genomics, and human nutrition.

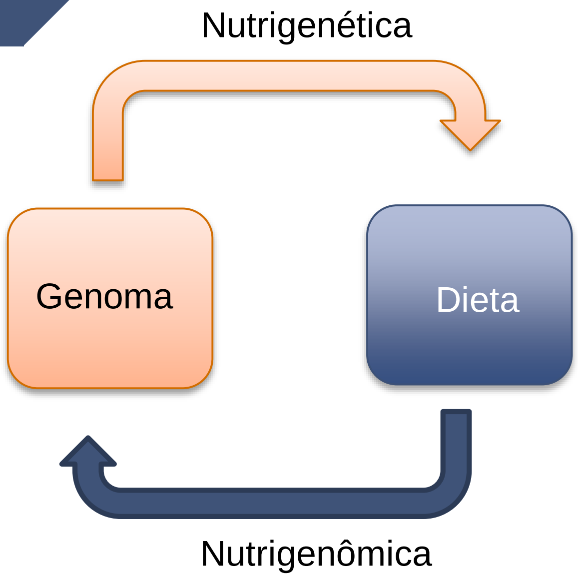
Desordens crônicas ligadas a nutrição

- Doenças cardiovasculares
- Câncer
- Obesidade
- Diabetes
- Desordens neurológicas
- Osteoporose
- Desordens inflamatórias

→ **Multifatoriais e multigênicas**

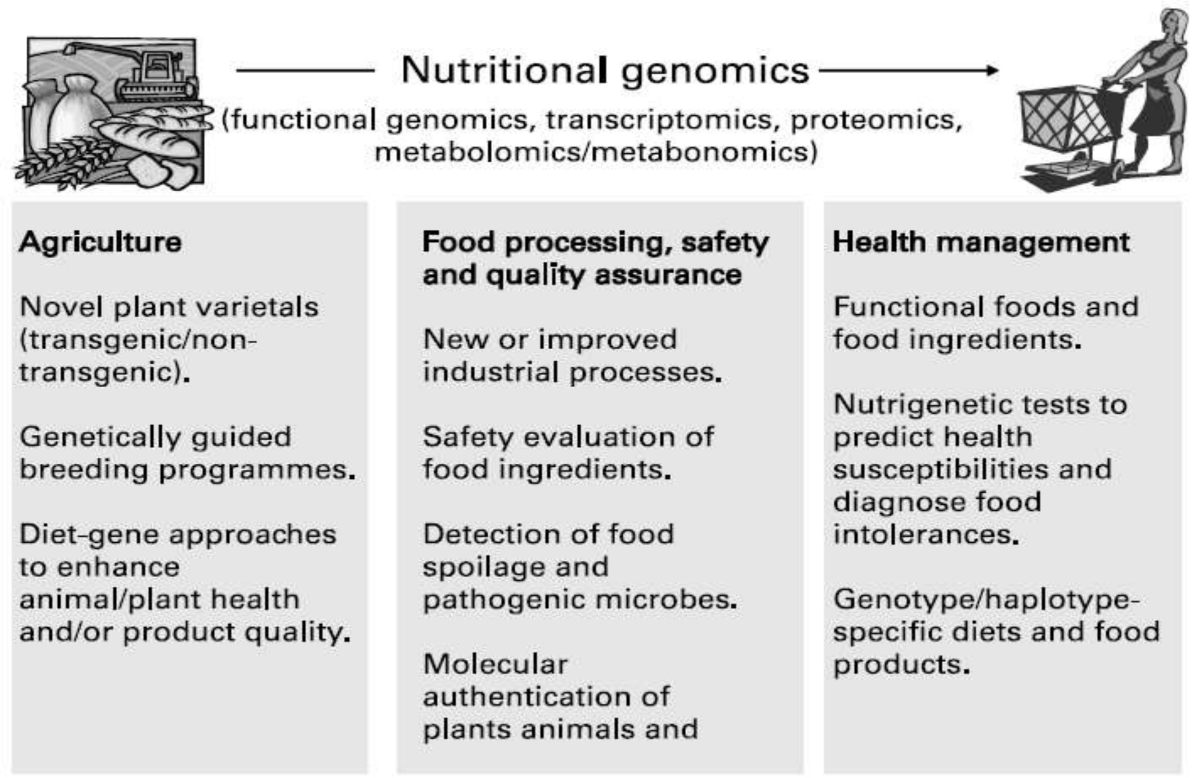
Genômica nutricional

- Duas disciplinas que estudam a interação dieta-genoma
- Nutrientes modulam a expressão gênica (ômicas)
- Características genéticas influenciam na interação com nutrientes (genômica)



Fonte: Debusk et al. (2004)

GN no agronegócio (*farm to fork*)



Fonte: Brown e van der Ouderaa (2006)

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NUTRIGENÉTICA

Nutrigenética

- Efeitos da variabilidade genética sobre a interação entre dieta e fenótipo
- Constituição genética influencia na resposta aos nutrientes de uma dieta
- Nutrição especializada para determinados genótipos

Popularização

Nutrigenética

- Diferenças genéticas (e epigenéticas) entre raças e dentro de raças
- Essas diferenças influenciam os requerimentos nutricionais, capacidade de ingestão, digestão, metabolização...
- Utilizar as novas tecnologias para identificar as diferenças
- Nutrição de precisão melhorando eficiência, sustentabilidade e saúde

Fonte: Neibergs and Johnson (2015)

Modelos matemáticos nutricionais

Livestock Science 190 (2016) 111–115

Contents lists available at ScienceDirect

Livestock Science

journal homepage: www.elsevier.com/locate/livsci

A new approach for applied nutritional models: Computing parameters of dynamic mechanistic growth models using genome-wide prediction

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ABSTRACT

Nutritional models have long been used as decision support tools by the livestock industry. Despite the advance of genomic prediction, these two disciplines have evolved separately. Because model parameters are responsible to describe between-animal variability, we propose an integration of nutritional models with genomics by means of such parameters. Two dynamic mechanistic models of cattle growth were used: Cornell Cattle Value Discovery System (CVDS) and Davis Growth Model (DGM). We estimated SNP marker effects for their parameters and also for observed phenotypes. Then, we compared what would be the best prediction scenario – model simulation with parameters computed from genomic data or genomic prediction directly on higher phenotypes. We found that genomic prediction on dry matter intake (DMI) and average daily gain (ADG) are still a better approach than using CVDS for predictions. Dry matter required (DMR), a CVDS-predicted value for DMI had higher correlation ($r=0.253$) with observed DMI than results from genomic prediction ($r=0.07$). DGM had better predictive ability ($r=0.38$) than genomic prediction on ADG ($r=0.098$). This is also the case for whole-body protein ($r=0.496$) and fat at slaughter ($r=0.505$) whose predictions were better with DGM than genomic prediction performed on the observed traits ($r=0.194$ and $r=0.183$, respectively). When contrasting simulations with genomically predicted parameters to those with regularly computed ones, CVDS showed moderate correlation and low bias between simulations of DMR ($r=0.966$; $b=0.9\%$) and ADG ($r=0.645$; $b=5.5\%$). Although further model development is necessary, the DGM with subject-specific parameters computed from genotypic data was a better option for predicting phenotypes than genomic prediction alone. In addition, simulations with genomically and regularly computed parameters match at a reasonable extend. This is the main argument to call attention from the research community that our approach may pave the way for the development of a new generation of applied nutritional models, especially towards individual-based simulations with subject-specific parameters computed from genomic information.

Highlights

- Genomic prediction on complex traits may still be better than from growth models.
- Genomically computed parameters agreeing with those obtained from regular methods.
- Growth models with genomic information may develop new applied nutritional models.

Hipóteses do desenvolvimento

- Humanos e modelos animais ➔ crescimento pré-natal na saúde quanto adultos

Resultaram em algumas importantes hipóteses:

- “Genótipo frugal” (Hales and Barker, 1992, 2001)

- “Plasticidade do desenvolvimento” (Bateson et al., 2004)

- “Programação fetal” (Barker, 1993, 2002)

David Barker 1938-2013

”...the serendipitous discovery...”
From obituary in Lancet 05 October 2013

WEIGHT IN INFANCY AND DEATH FROM ISCHAEMIC HEART DISEASE

D. J. P. Barker, P. D. Winter, C. Osmond, B. Margetts, S. J. Simmonds

MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO9 4XY

Summary Environmental influences that impair growth and development in early life may be risk factors for ischaemic heart disease. To test this hypothesis, 5654 men born during 1911–30 were traced. They were born in six districts of Hertfordshire, England, and their weights in infancy were recorded. 92·4% were breast fed. Men with the lowest weights at birth and at one year had the highest death rates from ischaemic heart disease. The standardised mortality ratios fell from 111 in

Lancet. 1989;2(8663):577-80.

Fenótipo/genótipo frugal

- *Thrifty genotype* ➔ "genótipo frugal" (NUTRIGENÉTICA)

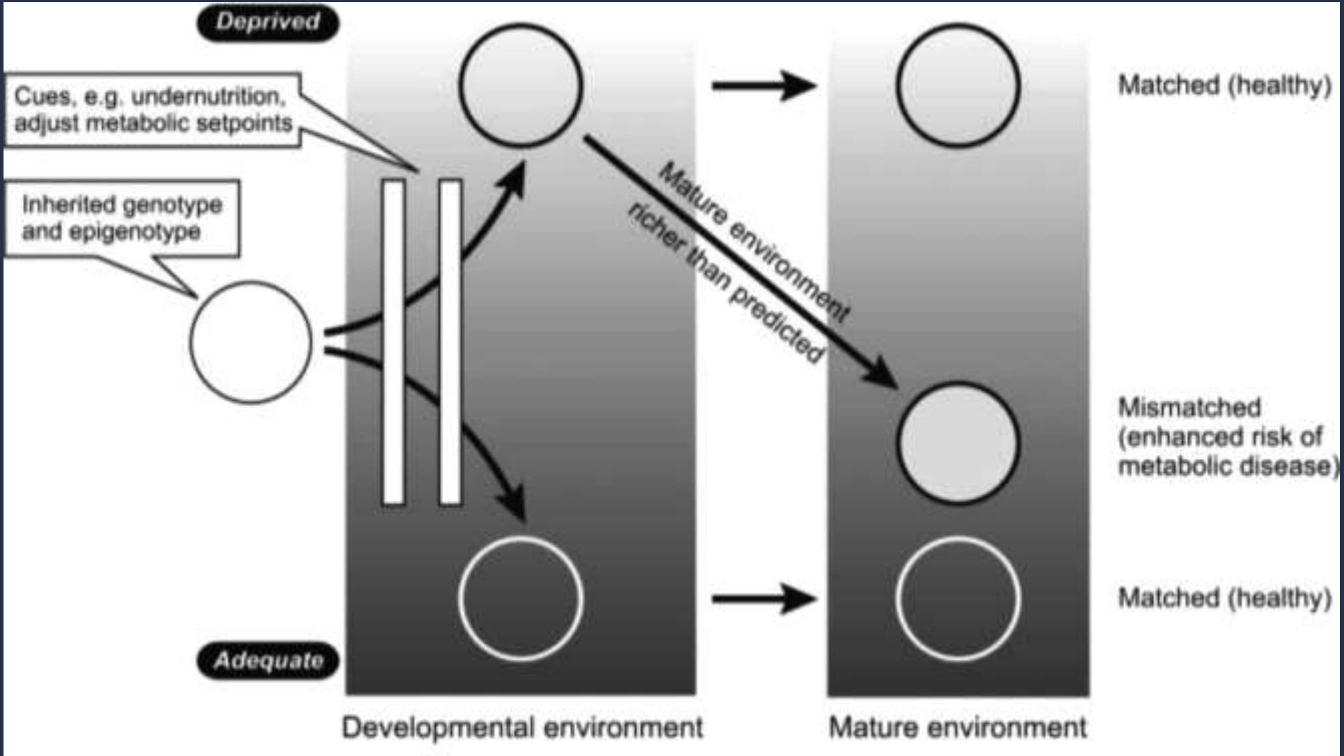
Seleção dos que possuem facilidade para acúmulo de gordura

Proteção contra baixa oferta de alimentos

- Aumento na obesidade

- Ingestão de calorias, períodos de escassez alimentar e atividade física

Genótipo Frugal (Genótipo x Ambiente)



Fonte: Hochberg et al. (2011)

Genótipo Frugal (Genótipo x Ambiente)

Livestock Science 229 (2019) 118–125

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journal homepage: www.elsevier.com/locate/livsci

ELSEVIER

Genomic evaluation of genotype by prenatal nutritional environment interaction for maternal traits in a composite beef cattle breed

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USDA Agricultural Research Service, Fort Keogh Livestock and Range Research Laboratory, Miles City, MT 59301 USA

A R T I C L E I N F O

Keywords:
Prenatal environment
SNP
Genetic correlation
Genotype-environment interaction

A B S T R A C T

Genes interact with both pre- and postnatal environments potentially affecting several important traits in beef cattle. The main objective of this study was to evaluate the existence of genotype by prenatal nutritional environment interaction using genomic information in growth traits, birth weight (BW), weaning weight (WW) and yearling weight (YW) in a composite beef cattle breed (50% Red Angus, 25% Charolais, and 25% Tarentaise). Dams were randomly assigned to be fed in two levels of harvested supplemental feed from Dec to March of each year that were expected to result in adequate (ADEQ) or marginal (MARG; ~ 61% of the supplemental feed provided by ADEQ) levels of protein based on average quality and availability of winter forage. This design resulted in two prenatal nutritional environments: MARG and ADEQ. A total of 3,020 records were used in a two-trait model treating each environment as a different trait. Genetic parameters for all three traits were estimated using genomic information. The direct genetic correlations between environment ADEQ and MARG were 0.97, 0.97 and 0.99 for BW, WW and YW respectively. On the other hand, the maternal genetic correlations between the two environments were 0.62, 0.41 and 0.73 for BW, WW and YW respectively. Furthermore, direct and maternal genomic estimated breeding values (GEBVs) using single step genomic BLUP were computed and the solutions of SNP markers were back solved from the resulting GEBVs to compare genomic regions associated with the two environments. The present study demonstrated the existence of maternal genetic by prenatal nutritional environment interaction especially for BW and WW in beef cattle.

Fonte: Hay and Roberts (2019)

Genótipo x Ambiente

- Interação dos genes com ambiente pré e pós-natal

- Avaliaram a relação genótipo x ambiente (nutrição pré-natal) no desempenho (PN, PD, P12)

- 2 tratamentos: ADEQ e MARG (61% PTN do ADEQ)

- 3020 bovinos compostos (50% angus, 25% Charolês e 25% Tarentaise)

Fonte: Hay and Roberts (2019)

Genótipo Frugal (Genótipo x Ambiente)

Existência da interação da nutrição pré-natal com o genótipo em bovinos de corte

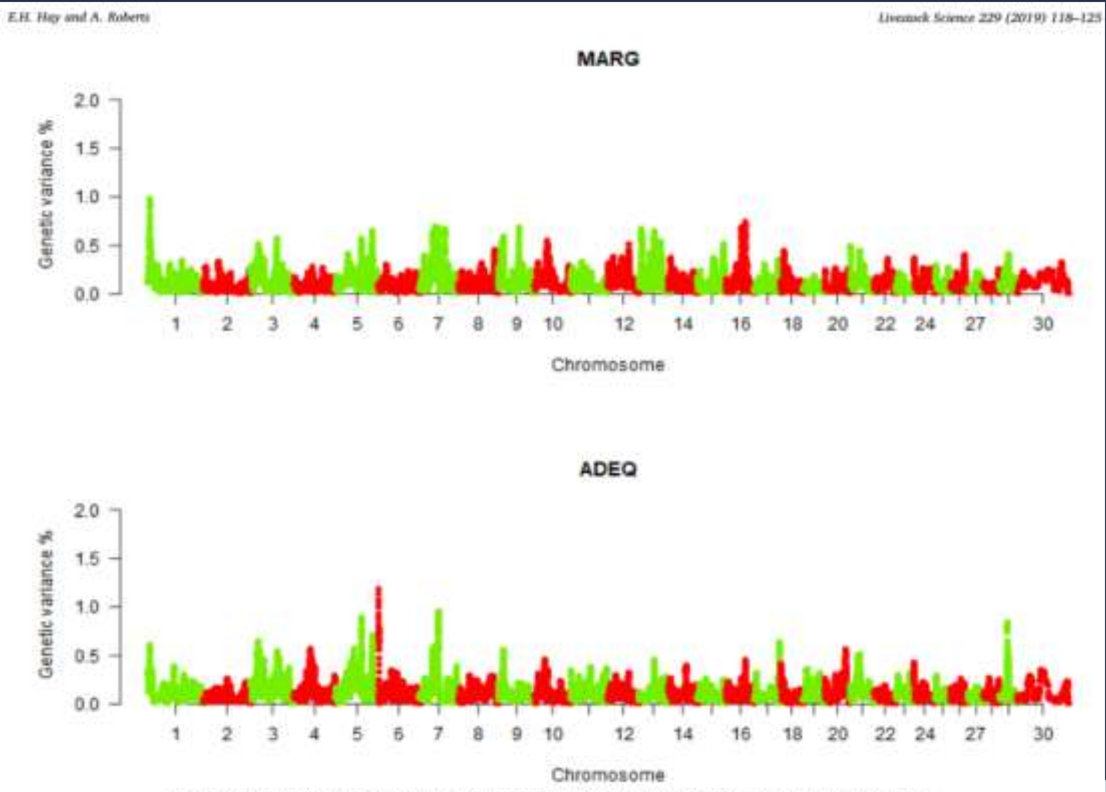


Fig. 5. Manhattan plot for maternal effect for yearling weight (YW) in ADEQ and MARG prenatal environments.

Fonte: Hay and Roberts (2019)

3

NUTRIGENÔMICA

Nutrigenômica

- Estuda a interação entre os nutrientes e os genes
- Nutrientes são moléculas bioativas
- **Nutrigenômica** é a ciência que estuda os efeitos da nutrição na expressão e função dos genes.

Nutrigenômica em bovinos

TRIENNIAL LACTATION SYMPOSIUM:

Pak J Biol Sci. 2014 Feb 1;17(3):329-34.

Nutrigenomics and its role in male puberty of cattle: a mini review.

Deb R, Chakraborty S, Mahima, Verma AK, Tiwari R, Dhama K.

Abstract

Nutrigenomics a novel era in genomics research is based on puzzling issue on how nutrition and genes re-interacts. Perusal of literature reveals that very few information are available in this field and especially when it is associated with puberty in cattle which is a multigenic trait of great economic importance. Thus it opens a new area of research interest. Various markers like-gonadotropin releasing hormone/GNRH (responsible for sexual differentiation and reproduction), interstitial growth regulating factor/IGF1 (having signal controlling reproduction function linked to somatic growth); circulating metabolic hormones viz., leptin apart from GnRH and IGF1 (having impact on testicular development in peripubertal bull) are proved to be associated with male puberty in cattle. Various minerals (copper, selenium, manganese, zinc, chromium, iron and molybdenum) and vitamins (Vit. A, D, E and C) are directly or indirectly linked to male puberty. But no research till today initiated how the nutrients effect on the transcriptome/proteome/metabolome level of marker genes associated with male puberty in cattle. Application of nanotechnology to make food safer for promotion of good health has created much excitement and nanoparticles has been developed against infectious diseases (e.g., Campylobacteriosis) affecting puberty along with certain nanocarriers that can facilitate the uptake of essential nutrients associated with puberty. Much of nutrigenomics research is however in infancy and hence the present mini-review will allow building the concept among researchers and scientists to initiate research in this interesting area.

transcription factors at play in controlling the nutrigenomic responses. Fatty acids, AA, and level of feed and energy intake have the strongest nutrigenomic potential. The effect of *t*10,*c*12 CLA on depressing

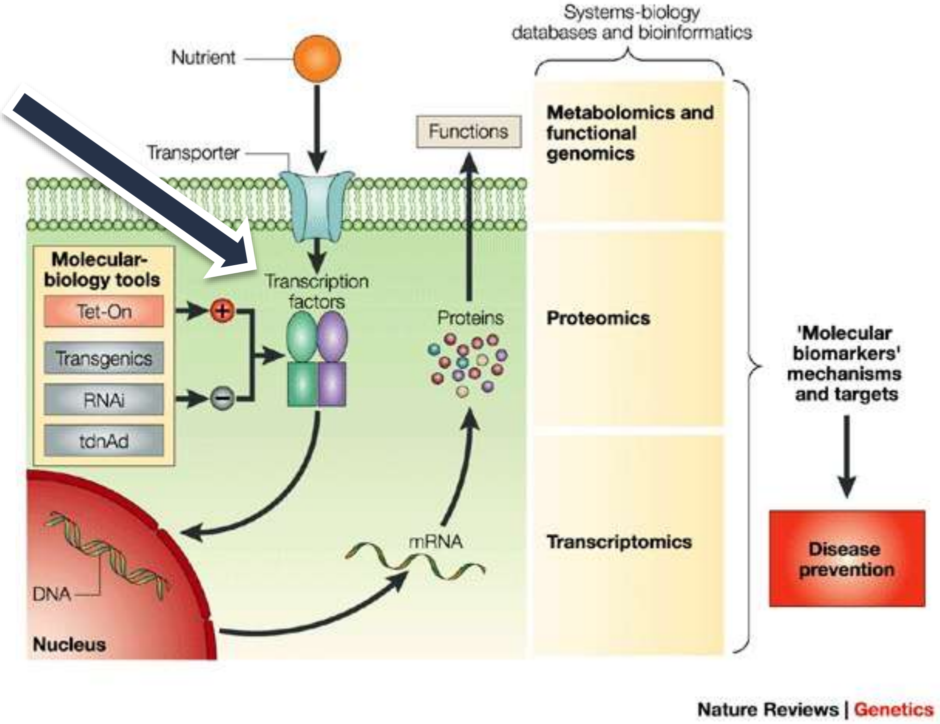
enomics era in ruminants and initial data strongly indicate that this scientific branch (and spinoffs such as nutriepigenomics) can play a critical role in future strategies to better feed dairy cattle.

Key words: dairy cow, long-chain fatty acids, nutrigenomics, transcription factor

Como os nutrientes alteram a expressão gênica?

Fonte: Müller and Kersten (2003)

Sinalização celular



Fonte: Müller and Kersten (2003)

Fatores de Transcrição

- SREBP

Proteínas de ligação do elemento de regulação do esterol

- ChREBP

Proteínas de ligação do elemento de resposta sensível a carboidratos

- PPAR

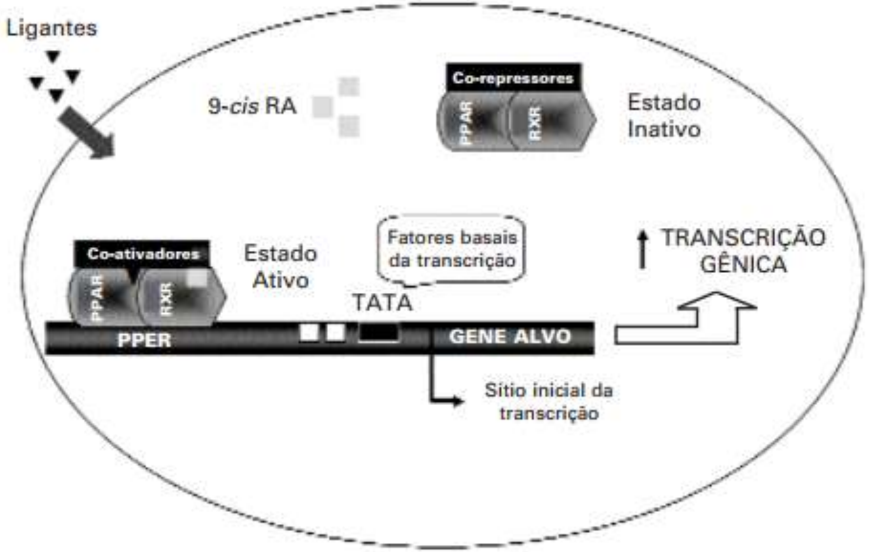
Receptores ativados por proliferador de peroxissoma

Nutrient	Compound	Transcription factor
Macronutrients		
Fats	Fatty acids Cholesterol	PPARs, SREBPs, LXR, HNF4, ChREBP SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
Micronutrients		
Vitamins	Vitamin A Vitamin D Vitamin E	RAR, RXR VDR PXR
Minerals	Calcium Iron Zinc	Calcineurin/NF-ATs IRP1, IRP2 MTF1
Other food components		
	Flavonoids Xenobiotics	ER, NFκB, AP1 CAR, PXR

Fonte: Müller and Kersten (2003)

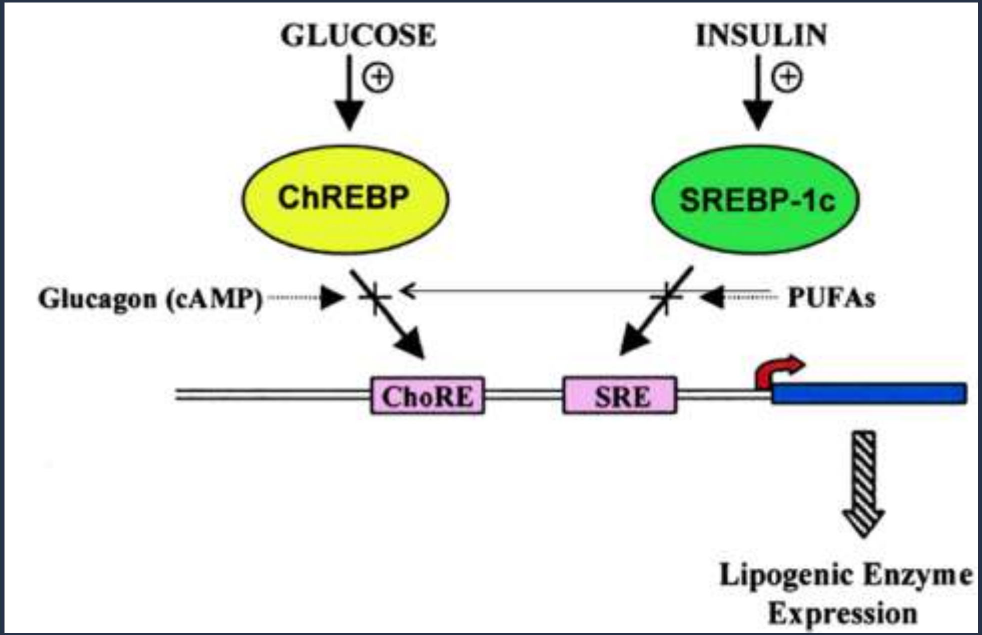
PPAR

- PPAR se acopla ao RXR (receptor X retinóide)
- Juntos ativam genes do metabolismo lipídico, homeostase da glicose, balanço energético e inflamação
- Os ácidos graxos e seus derivados são importantes ligantes do PPAR

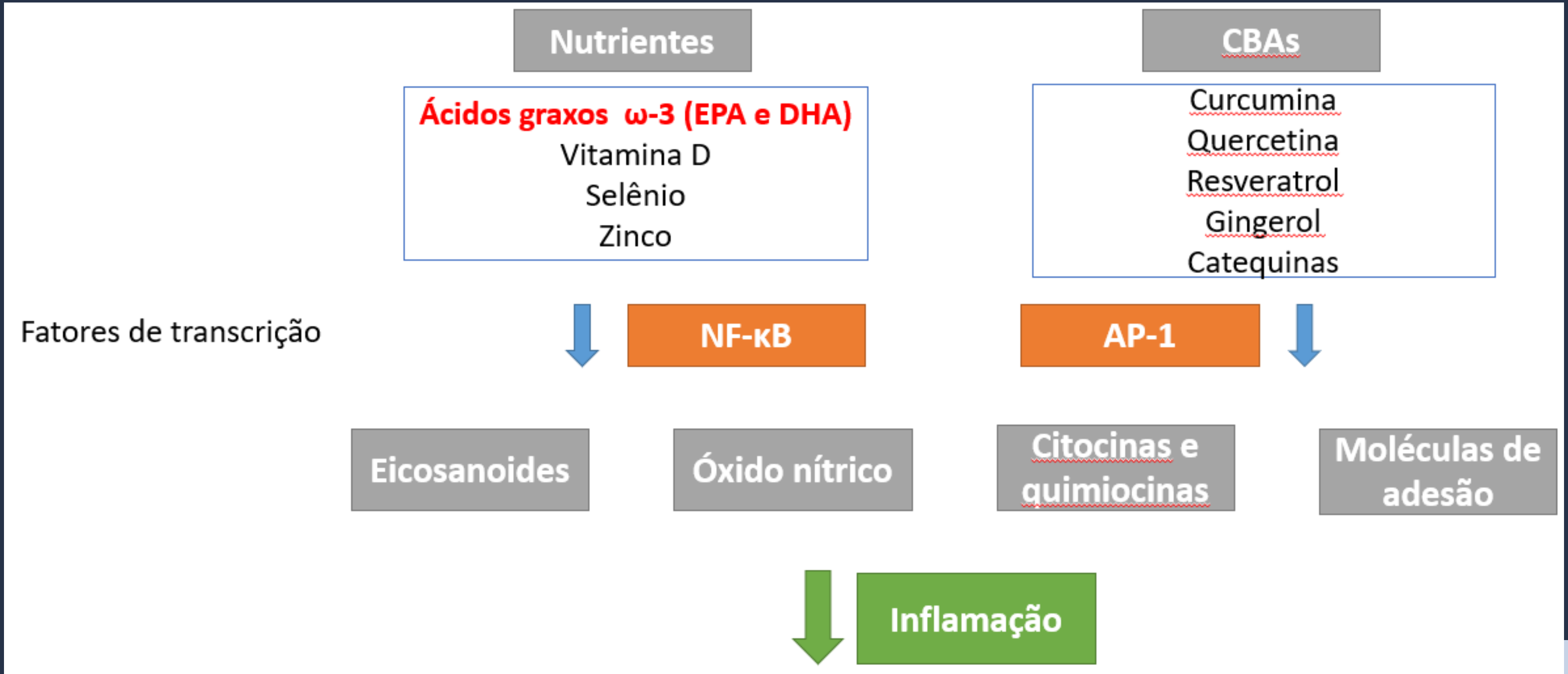


Fatores de transcrição e metabolismo

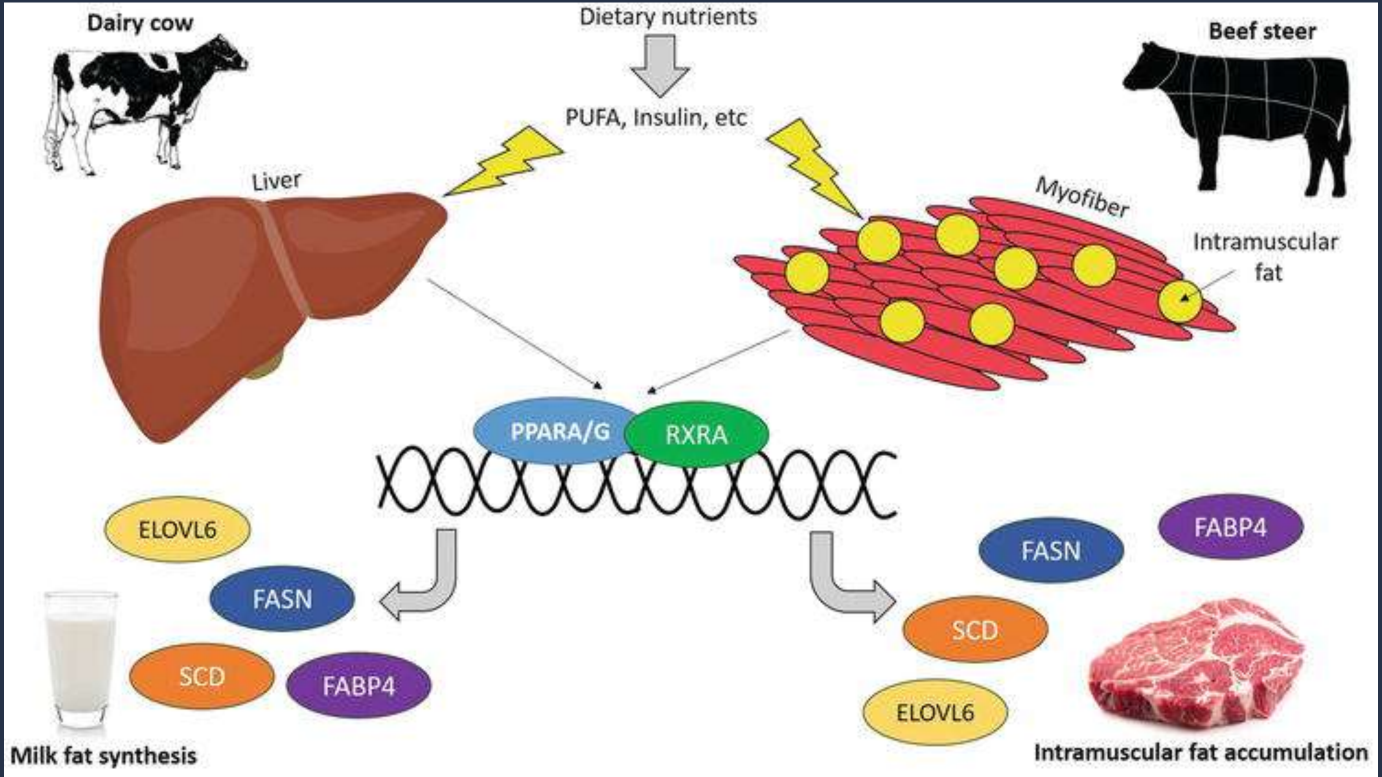
Genes importantes na lipogênese respondem ao SREBP (colesterol, AG e insulina) e ChREBP (glicemia)



Compostos bioativos



Aplicação nutrigenômica Leite x Carne

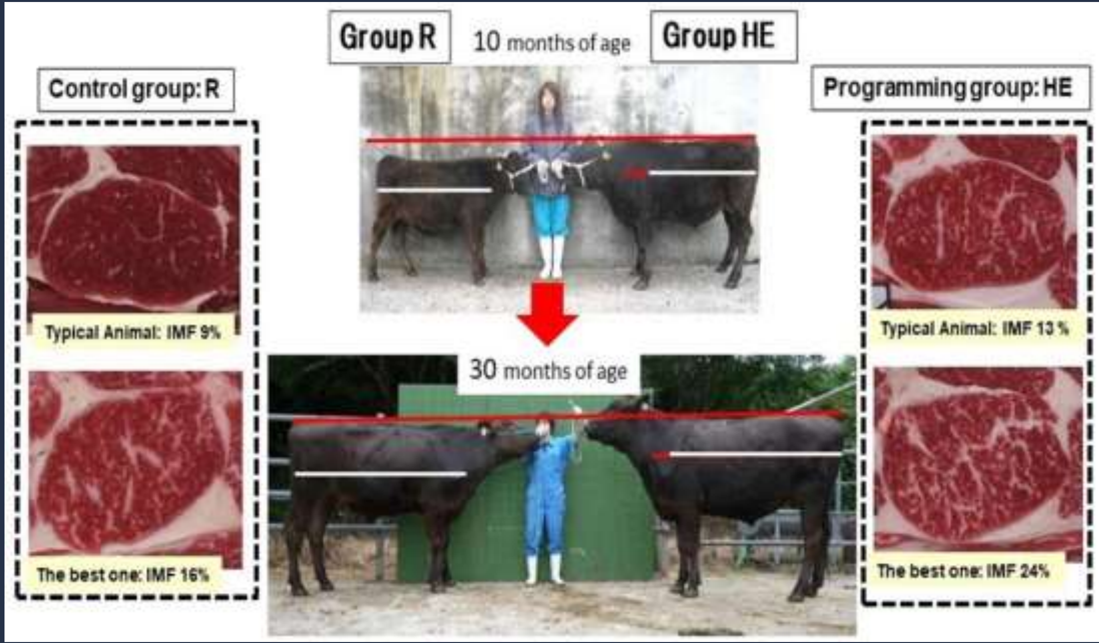


Fonte: Osorio e Moisa (2018)

Efeito no "residual" em Wagyu

Grupo HE dieta rica em substituto de leite dos 4 aos 10 meses de idade

Dos 10 meses aos 30 meses a mesma dieta (pastagem)



Fonte: Gotoh et al. (2018)

Hipóteses do desenvolvimento

- Humanos e modelos animais ➔ crescimento pré-natal na saúde quanto adultos

Resultaram em algumas importantes hipóteses:

- “Genótipo frugal” (Hales and Barker, 1992, 2001)

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Lancet. 1989;2(8663):577-80.

Programação fetal

- Estímulo/insulto nutricional pré-natal visando alterações fenotípicas na progênie
- Modular a nutrição materna para alterar à longo prazo de sua progênie e alé

Fonte: Du et al. (2011)

Crescimento fetal

- Fatores que podem afetar o crescimento fetal, desenvolvimento e peso ao nascimento bovino:

- Tamanho placental e capacidade de transferência de nutrientes

- Ordem de parto, idade e tamanho da matriz

- Genótipo materno, paterno e fetal

- Temperatura ambiental e época do nascimento

- Nutrição materna

Fonte: Robinson et al. (2014)

Aplicação prática

27/03/2018

15/07/2018

Fonte: Próprio autor

Programação fetal

- Repartição de nutrientes:

Cérebro, coração, fígado e rins

- Músculo esquelético e tecido adiposo têm baixa prioridade e são vulneráveis à mudanças nutricionais
- Usar a programação pra melhorar a composição corporal

Fonte: Zhu et al. (2006)

Programação fetal

Terço final de gestação (75% crescimento fetal):

- Melhorou saúde e lucratividade na terminação (suplementação proteica)
- Maior peso à desmama de novilhas (232 vs. 225 kg, suplementação proteica)
- Maior peso à desmama novilhos (>5-10 kg, suplementação proteica)
- Maior peso, fertilidade de bezerras pós-desmama

Fonte: Mulliniks et al. (2013), Funston et al. (2010), Stalker et al. (2007), Martin et al. (2007)

Miogênese e adipogênese

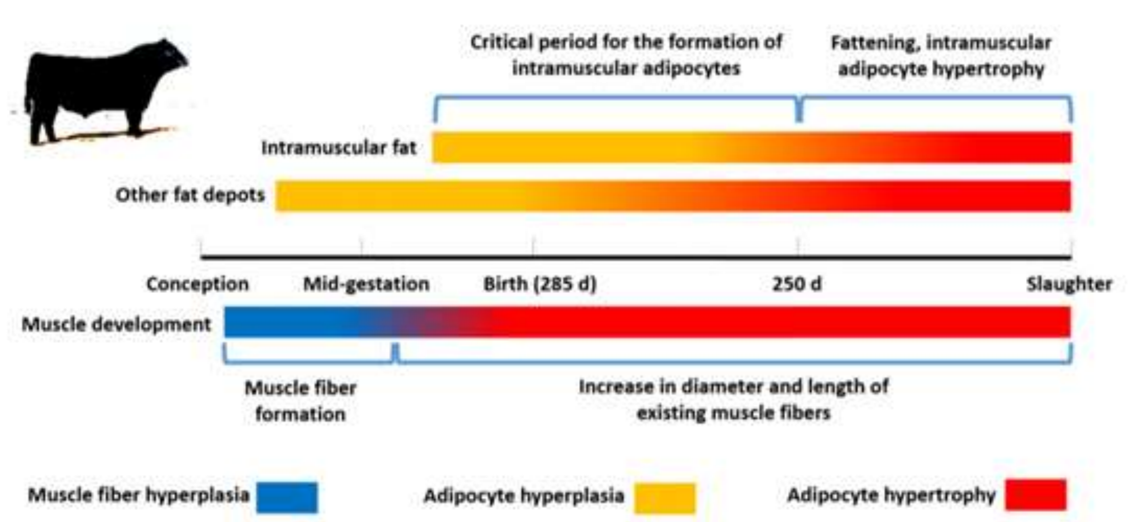


Figure 1. Timelines for skeletal muscle and adipose tissue development in beef cattle and pigs. The times for muscle fiber hyperplasia and hypertrophy and adipocyte hyperplasia and hypertrophy are approximate.

Fonte: Du et al. (2017)

Interação entre nutrientes e genes

Interações Diretas

Nutrientes interagem com receptor (F.T.) modificando expressão gênica

Interações Indiretas

Nutrientes modificam a "estrutura" do acesso ao DNA que altera a expressão gênica (crônico)

4

NUTRIEPIGENÉTICA

Epigenética

- Mudanças na expressão gênica sem alterar a sequência do DNA
- Relativamente estáveis e potencialmente herdáveis (longo prazo, transgeracional)
- Fatores ambientais (nutrição) regulam o epigenoma e estes podem influenciar a expressão gênica

Dano ao DNA por deficiência de micronutrientes

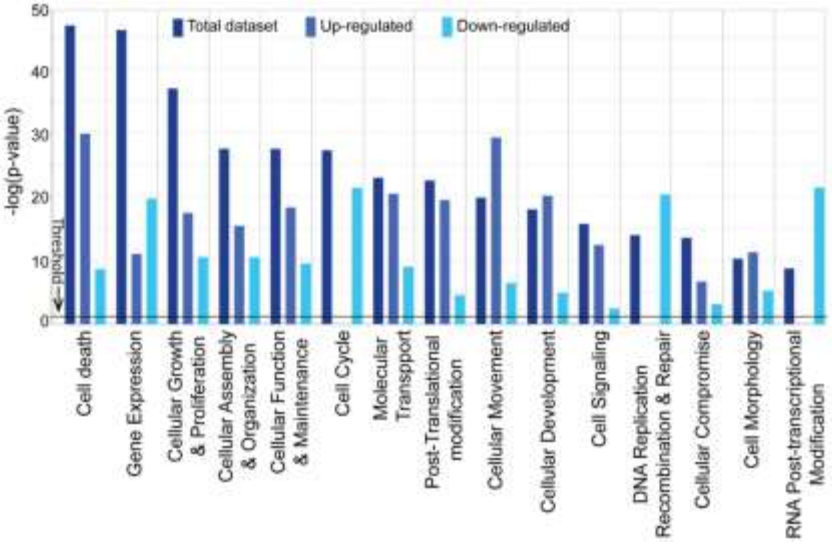
Table 3. *Micronutrient deficiency and DNA damage*

Micronutrient	Percent of US Population	DNA Damage	Health Effects
Folic acid	10%	Chromosome breaks	Colon cancer; heart disease; brian dysfunction
Vitamin B_{12}	4% (<half RDA)	Uncharacterized	Same as folic acid; neuronal damage
Vitamin B_6	10% (<half RDA)	Uncharacterized	Same as folic acid
Vitamin C	15% (<half RDA)	Radiation mimic (DNA oxidation)	Cataracts (4×); cancer
Vitamin E	20% (<half RDA)	Radiation mimic (DNA oxidation)	Colon cancer (2×); heart disease (1.5×); immune dysfunction
Iron	7% (<half RDA) 19% women 12–50 yr old	DNA breaks; radiation mimic	Brain and immune dysfunction; cancer
Zinc	18% (<half RDA)	Chromosome breaks; radiation mimic	Brain and immune dysfunction; cancer
Niacin	2% (<half RDA)	Disables DNA repair (polyADP ribose)	Neurological symptoms; memory loss

Fonte: Kaput et al. (2004)

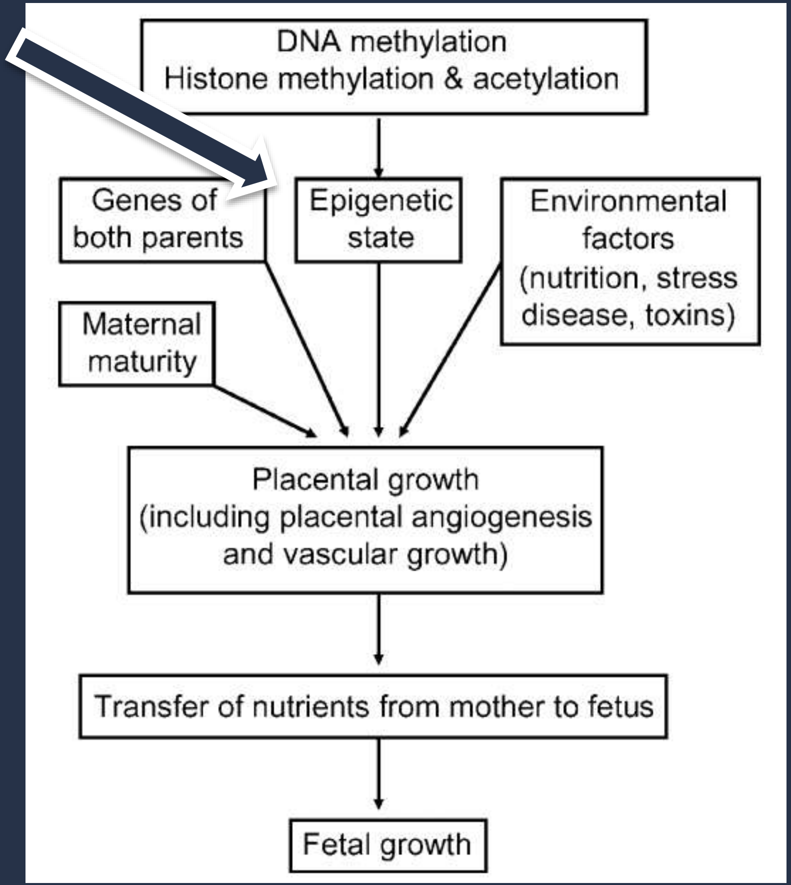
Epigenética

- Indução epigenética na inibição da histona desacetilase (HDAC) pelo butirato
- Butirato induz a hiperacetilação das histonas
- Butirato induz a regulação epigenômica nas células bovinas



Fonte: Li e LI (2006); Wu et al. (2012)

Crescimento fetal



Fonte: Wu et al. (2006)

Nutriepigenética

Epigenetics: Setting Up Lifetime Production of Beef Cows by Managing Nutrition

R.N. Funston and A.F. Summers

West Central Research and Extension Center, University of Nebraska, North Platte, Nebraska 69101; email: rfunston2@unl.edu; adamfsummers@gmail.com

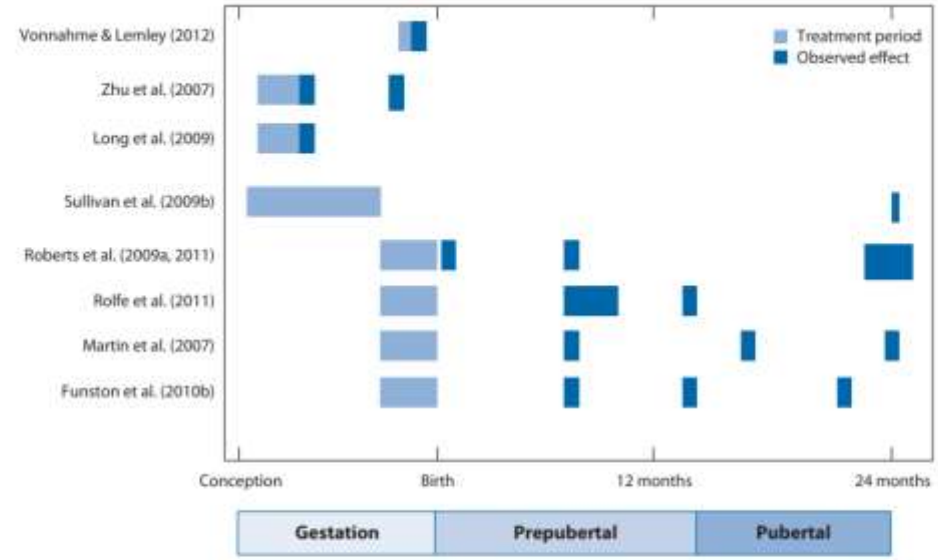


Figure 1

Timing of maternal nutrient alteration (*light blue*) impacts fetal development and progeny performance (*dark blue*) in beef cattle. Adapted from Rhind et al. (70).

Fonte: Funston & Summers (2013)

Nutriepigenética

Table 3 Effect of maternal protein supplementation on heifer progeny performance

Item	Dietary treatment			
	Martin et al. (99)[a]		Funston et al. (100)[b]	
	NS	SUP	NS	SUP
Birth weight, kg	35	36	35	35
Weaning weight, kg	207	212	225[d]	232[e]
Adj. 205-day weight, kg	218[d]	226[e]	213	217
Dry matter intake, kg/day	6.50	6.75	9.48	9.30
Average daily gain, kg/day	0.41	0.40	0.85	0.79
Residual feed intake	−0.12	0.07	0.08	−0.04
Final BW[c], kg	290[x]	304[y]	—	—
Age at puberty, day	334	339	366[x]	352[y]
Prebreeding weight, kg	266[d]	276[e]	317	323
Pregnancy diagnosis weight, kg	386[d]	400[e]	364	368
Pregnant, %	80[d]	93[e]	80	90
Calved in first 21 d, %	49[d]	77[e]	85	77

Fonte: Funston & Summers (2013)

Nutriepigenética

- Os processos da metilação de DNA dependem de doadores de grupo metil
- Ex: colina, betaina, vit B12, ácido fólico, metionina

- Efeito da restrição de Met e Vit B em ovelhas prenhez

Alterações na metilação do DNA dos cordeiros durante toda sua vida

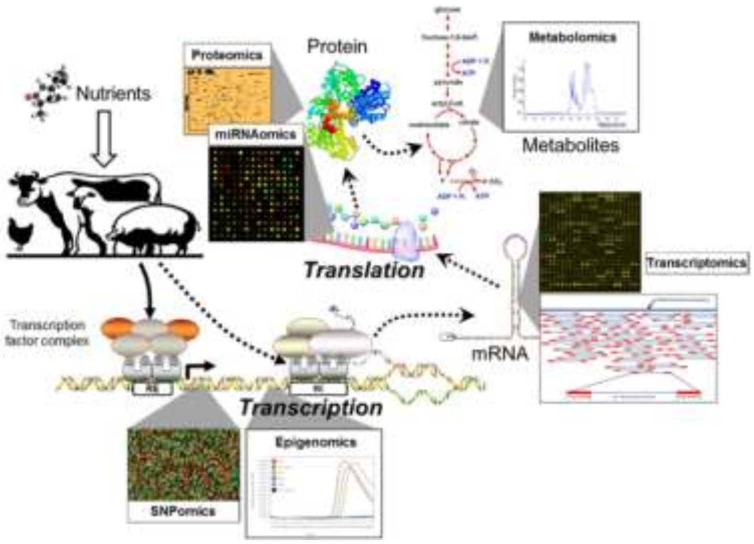
Piores condições de saúde e bem-estar, resistência à insulina, maior pressão sanguínea e alterações na resposta imune

Progênie das fêmeas suplementadas tiveram alterações na gordura subcutânea e no crescimento muscular

Fonte: Lan et al. (2013); Penagaricano et al. (2014); Osorio et al. (2017)

Genômica nutricional da vaca gestante

- **Genética** e **Nutrição** devem ser estudadas em conjunto
- Tudo passa pela melhor compreensão das **interações** gene-dieta (diretas ou **indiretas**)
- Olhar holístico pra matriz bovina gestante e suas progênies



OBRIGADO!

Perguntas?

Podem me contatar em **mhasantana@usp.br**

gopec.usp