GISMO 2022

XVIII CONGRESSO NAZIONALE

FRAGILITÀ MUSCOLO-SCHELETRICA
STILI DI VITA E APPROPRIATEZZA TERAPEUTICA
LE SFIDE PER IL FUTURO

Baveno
7 - 8 ottobre 2022

GISMO

Gruppo Italiano Studio
Malattie Metabolismo Osseo

- Osteoporosi
- Malattie Muscolo-Scheletriche
- Malattie Metaboliche
- Dolore
- Nutrizione

Professor Iacopo Chiodini

Università degli Studi di Milano

I rapporti muscolo-osso: dalla fisiopatologia alla clinica

AGENDA: I rapporti muscolo-osso: dalla fisiopatologia alla clinica

- **Premesse**
- **Osteocalcina**
- **Miostatina, IL6**
- **Irisina**
- **Lipocalina 2**
- **Conclusioni**

Bone and Muscle Endocrine Functions: Unexpected Paradigms of Inter-organ Communication

Cell *164*, March 10, 2016

Gerard Karsenty[1,*] and Eric N. Olson[2,3]

- The **destruction, or resorption**, of bone must be energetically demanding since it **occurs daily in multiple locations in one of the largest organs in the body**.
- Since **bone formation** requires that osteoblasts synthesize and secrete daily, large amounts of proteins to form the ECM, it **is also likely to be energetically expensive**.
- This constant alternation of bone destruction and bone formation fulfills biological functions of fundamental importance: bone modeling allows the **longitudinal growth of the skeleton during childhood and therefore the ability to stand, walk, and run and consents to repair micro- and macrodamages**
- The hypothesis that bone (re)modeling **is an energetically costly** physiological process becomes a reality when looking at clinical situations: when access to food—i.e., energy—is limited, bone growth stops in children and bone mass decreases in adults

The powerful influence of food/energy intake on bone (re)modeling revealed by clinical observations raises two questions:

I QUESTION: If energy intake is so important for bone, does bone in turn regulate energy metabolism, or is bone an endocrine organ regulating energy metabolism?

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II QUESTION:

Why evolution came up with an invention as energetically costly as bone precisely at a time when food was so scarce?

Possible (not mutually exclusive) answers:

1) Bone confers an evolutionary advantage to animals living on land by the ability to stand, walk, and run.
2) Bone fulfills important aspects of energy metabolism.
3) Bone may regulate other important physiological functions (fertility).

Gerard Karsenty and Eric N. Olson, Cell 2016

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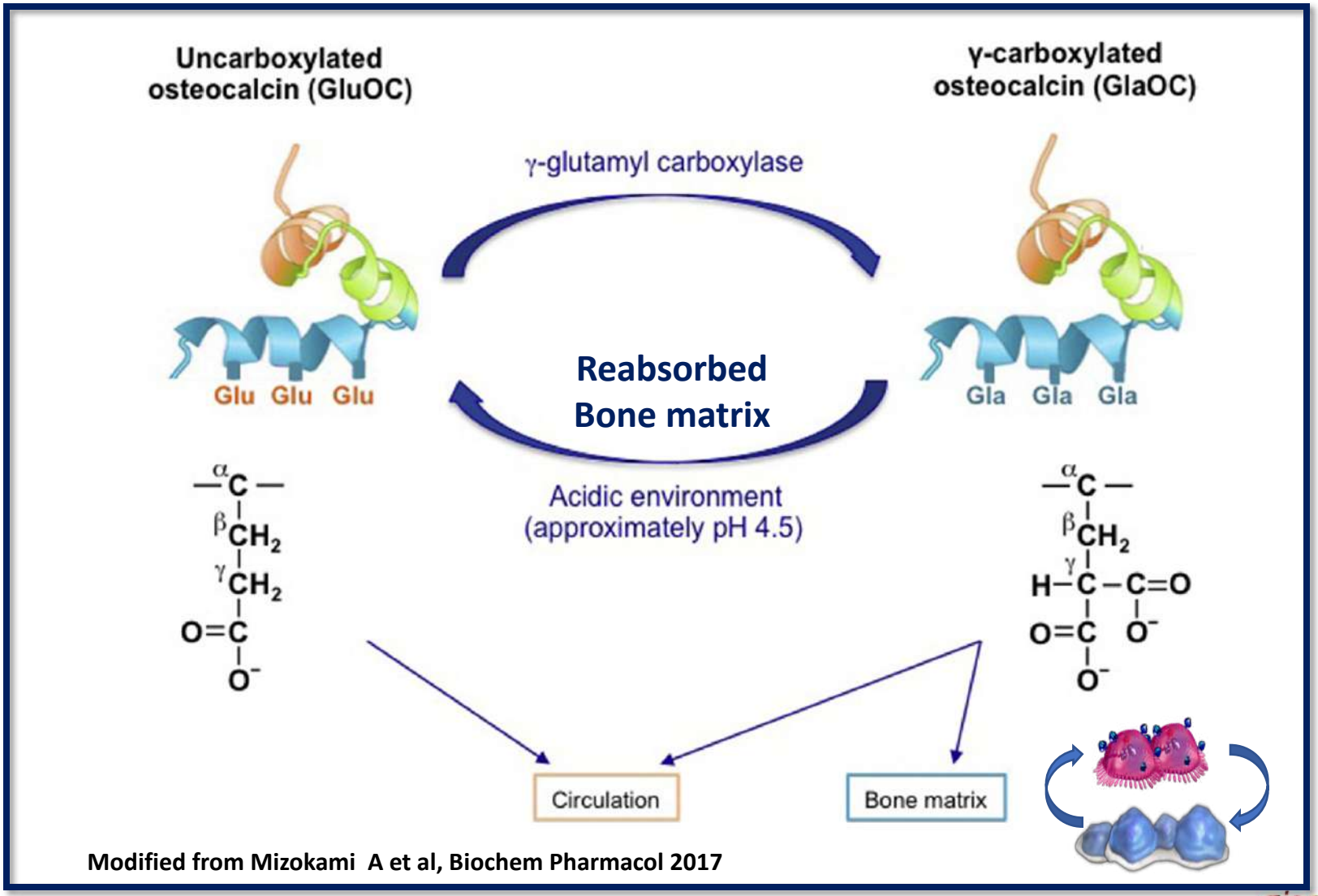
OSTEOCALCIN
An osteoblast secreted hormone



Modified from Mizokami A et al, Biochem Pharmacol 2017

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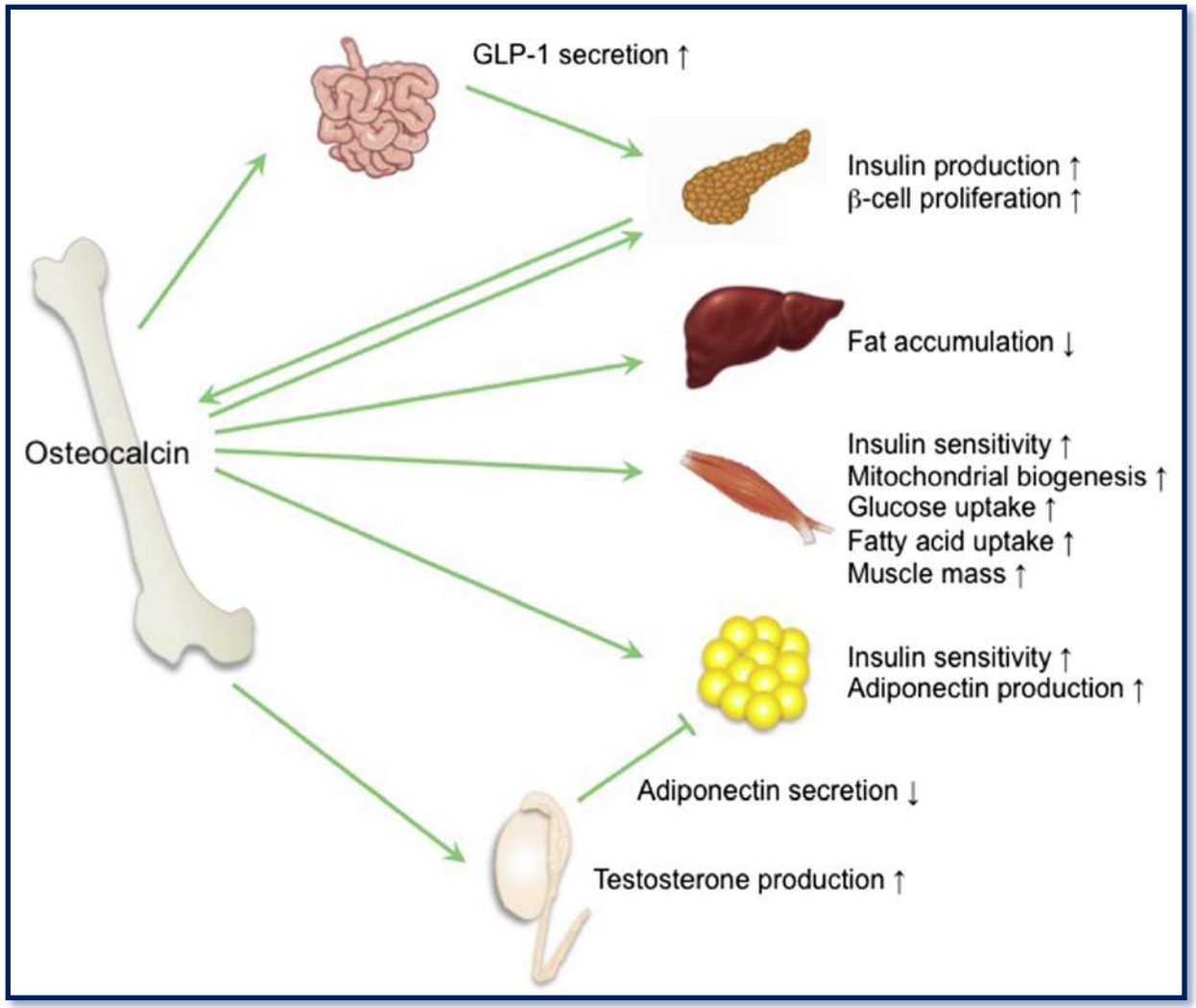
OSTEOCALCIN IS A HORMONE



A. Mizokami et al, Biochemical Pharmacology 2017

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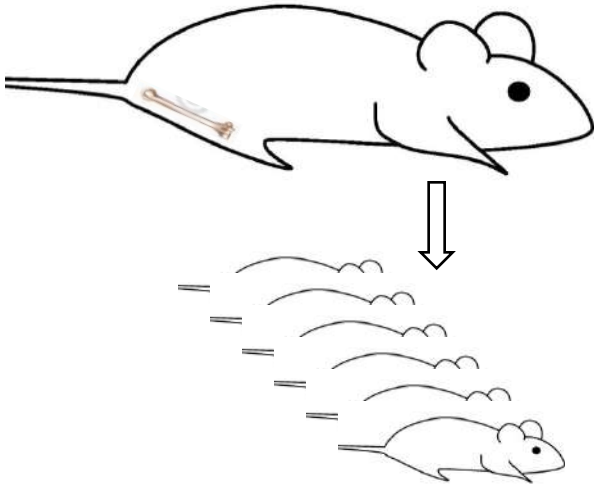
OSTEOCALCIN (OC) HISTORY

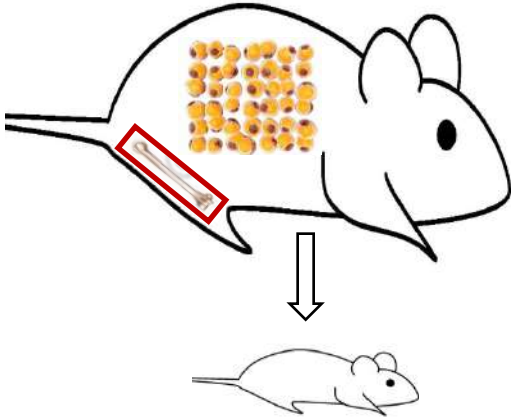
Putatively involved in the site-specificity (bone and teeth but not other collagen-rich tissues) of extracellular matrix (ECM) mineralization, since:

- **OC is an osteoblast-specific protein secreted in large amounts in the bone ECM**
- **OC genes are expressed during development around the time mineralization begins**
- **Gamma carboxylation of 3 glutamic acid residues gives high affinity for mineral ions**

***Osteocalcin* WT**



***Osteocalcin*$^{-/-}$**



Osteocalcin-deficient mice:

- **had a dramatic increase in abdominal fat**
- **started to breed later and became infertile sooner**

The OC inactivation or overexpression in osteoblasts or other cells had any effects on bone

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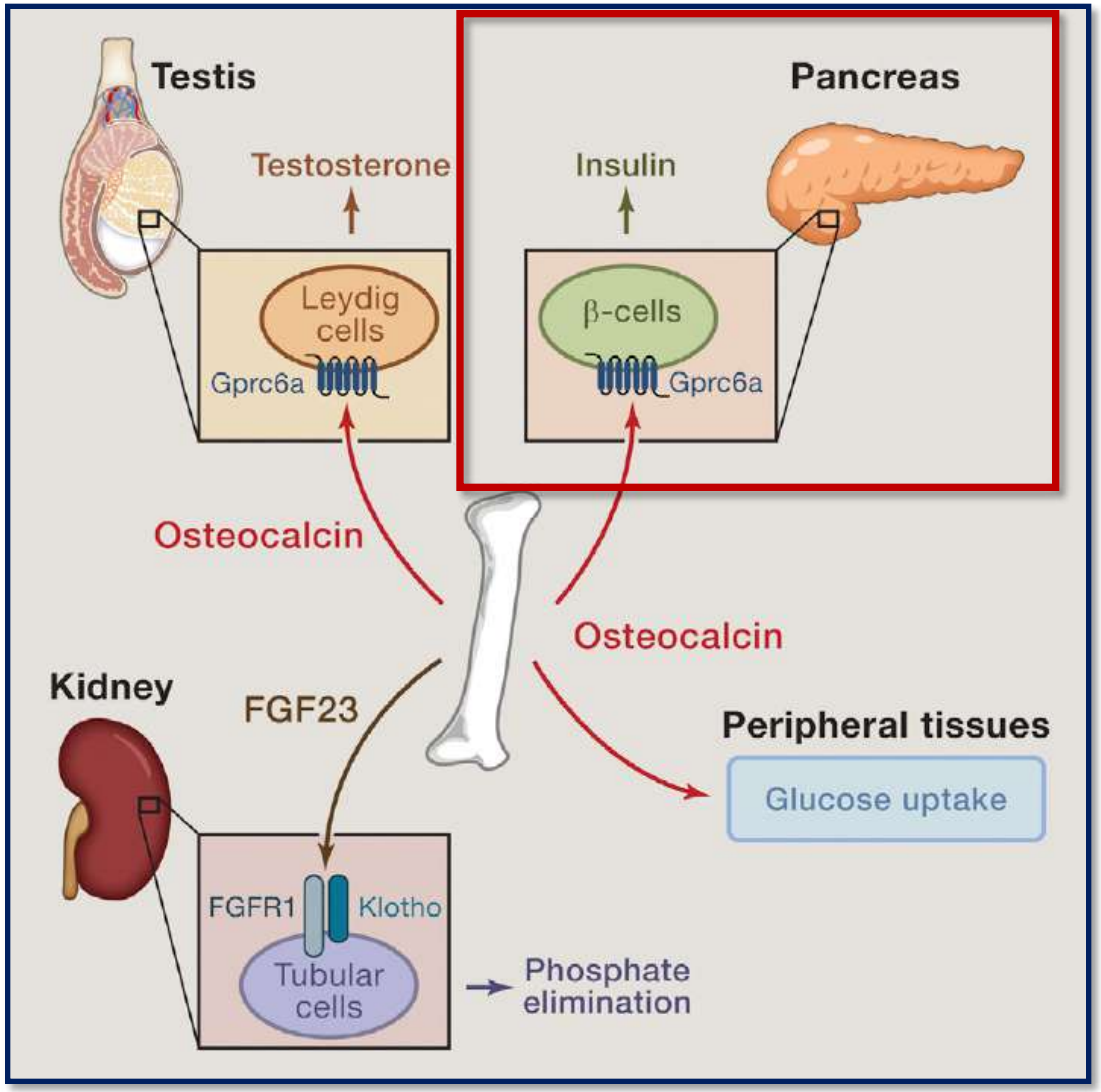
ENDOCRINE ROLES FOR OSTEOCALCIN



Karsenty G & Olson N, Cell 2016

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UNCARBOXYLATED OSTEOCALCIN IS AN OSTEOBLAST DERIVED HORMONE THAT AFFECTS β-CELLS

IN VIVO (ANIMAL) STUDIES	
Loss of function studies	**Gain of function studies**
Reduced insulin secretion	Increased insulin secretion
Reduced β-cell proliferation	Increased β-cell proliferation
Reduced glucose tolerance	Increased glucose tolerance
Reduced insulin sensitivity	Increased insulin sensitivity
Reduced energy expenditure	Increased energy expenditure

Lee NK et al, Cell 2007

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UNCARBOXYLATED OSTEOCALCIN IS AN OSTEOBLAST DERIVED HORMONE THAT AFFECTS INSULIN AND ADIPONECTIN EXPRESSION

Human studies:

- Uncarboxylated osteocalcin increases the expression of the *Insulin* gene and of genes needed for β-cell proliferation (*Cyclind2* and *Cdk40)*

  Sabek OM et al, Endocrinology 2015.

- Circulating osteocalcin levels are inversely correlated with fasting glucose, insulin levels, BMI, and body fat.

  Fernandez-Real JM et al, J Clin Endocrinol Metab 2009.

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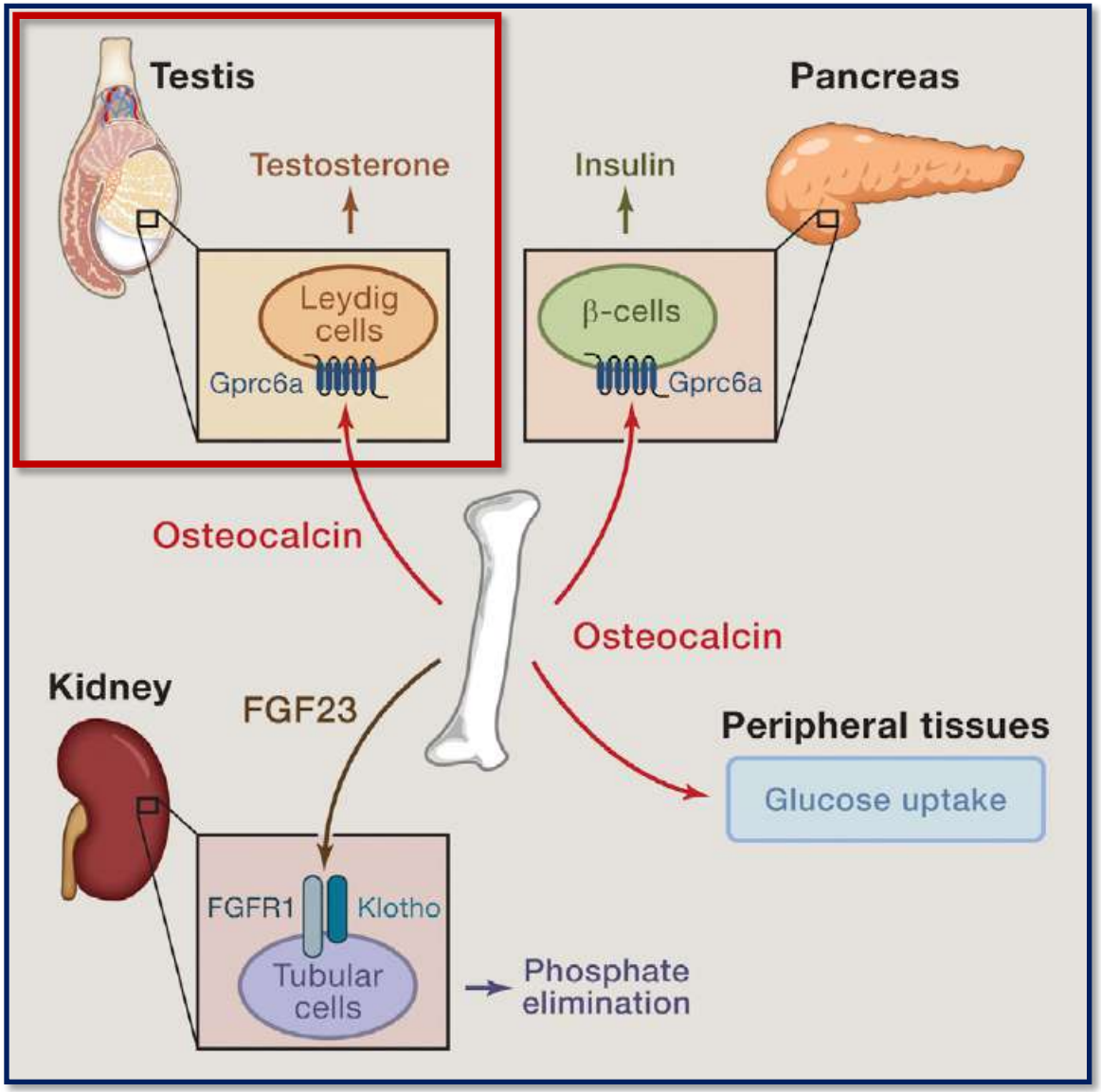

Karsenty G & Olson N, Cell 2016

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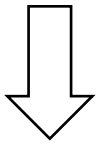
UNCARBOXYLATED OSTEOCALCIN IS AN OSTEOBLAST DERIVED HORMONE THAT FAVOURS REPRODUCTIVE FUNCTION

In vivo (animal)

Loss- and gain-of-function mouse models of osteocalcin function, as well as the treatment of Leydig cells with osteocalcin show that uOC:

- signals directly to Leydig cells to favor the expression of all genes encoding the enzymes necessary for testosterone synthesis
- does not affect the expression of Cyp19 (needed for T→ E2)



Male mice lacking osteocalcin show typical features of hypo-testosteronemia (low sperm count and lower weight of the epididymis and testes) and increased LH levels

Oury F et al, Cell 2011

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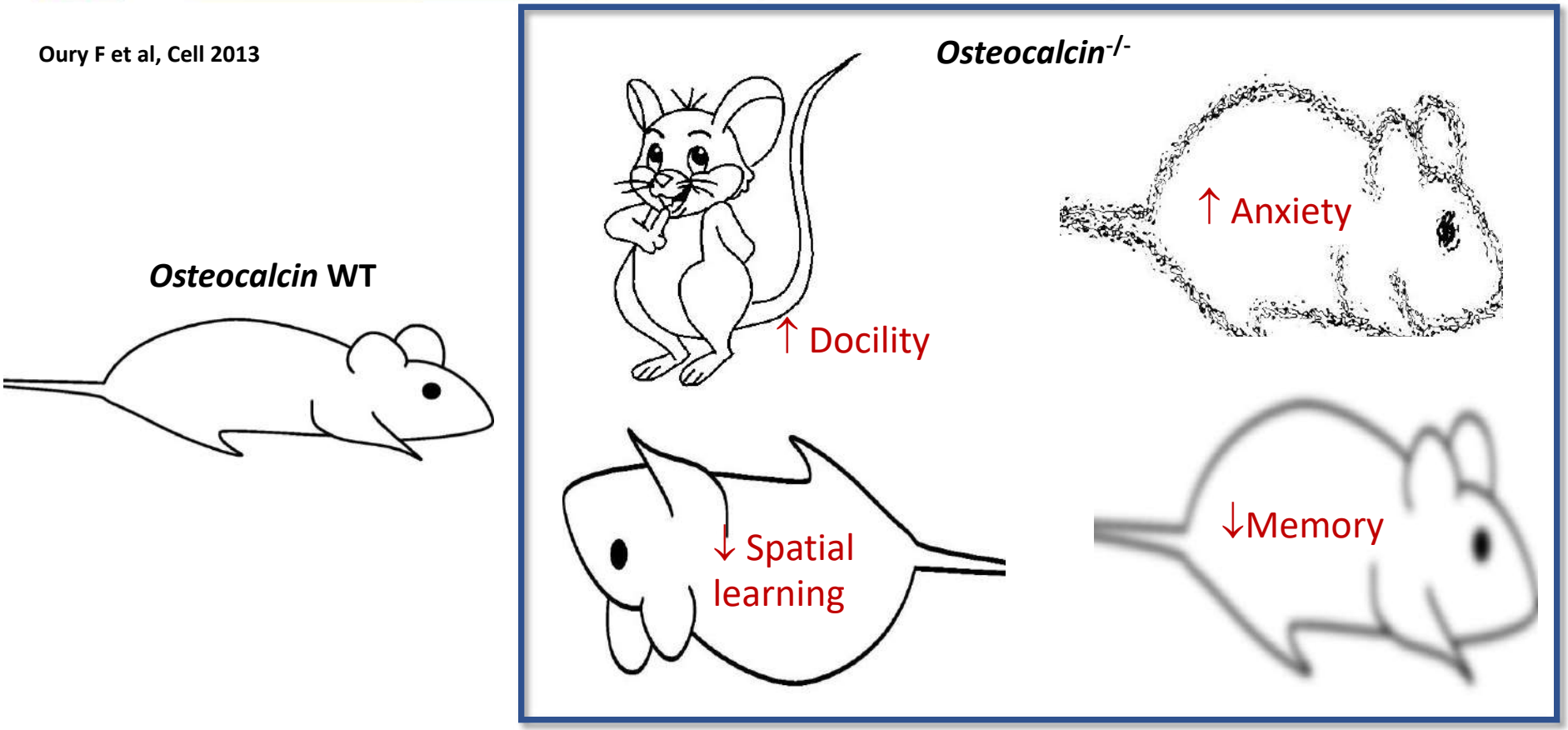
BONE INFLUENCES BRAIN TROUGH OSTEOCALCIN

Oury F et al, Cell 2013



- Decrease in the synthesis of all monoamine neurotransmitters and to an increase in GABA
- OC delivery in the brain through intracerebroventicular infusion corrects them.
- OC crosses the blood-brain barrier and binds specifically to serotonergic neurons of raphe nuclei in the brainstem and to neurons of the CA3 region of the hippocampus and of the dopaminergic nucleus of ventral tegmental area in the midbrain

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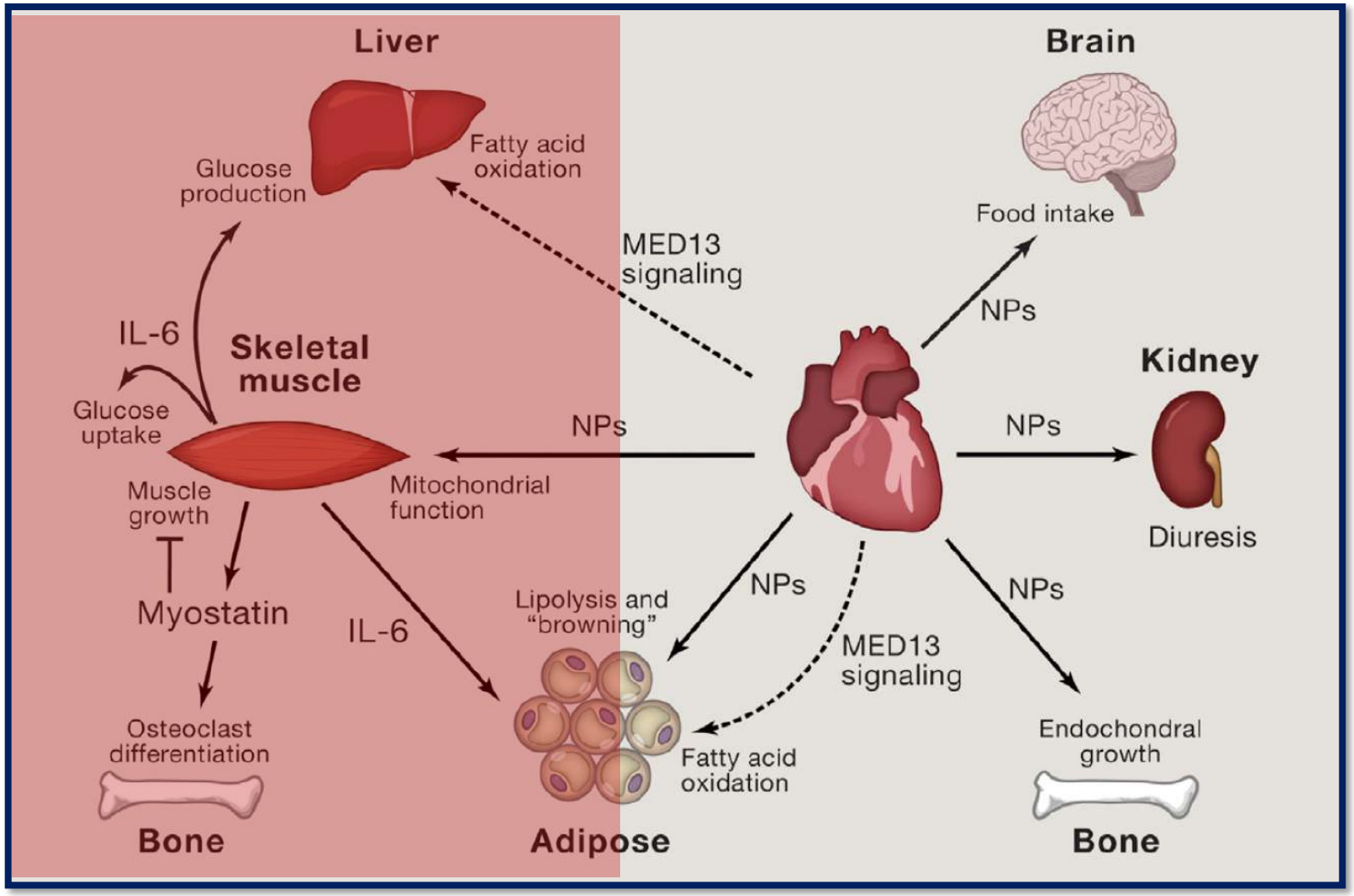
ENDOCRINE SIGNALS FROM STRIATED MUSCLES TO DISTAL TISSUES

Karsenty G & Olson N, Cell 2016



NPs: natriuretic peptides; IL-6: interleukin 6; MED13: mediator subunit 13

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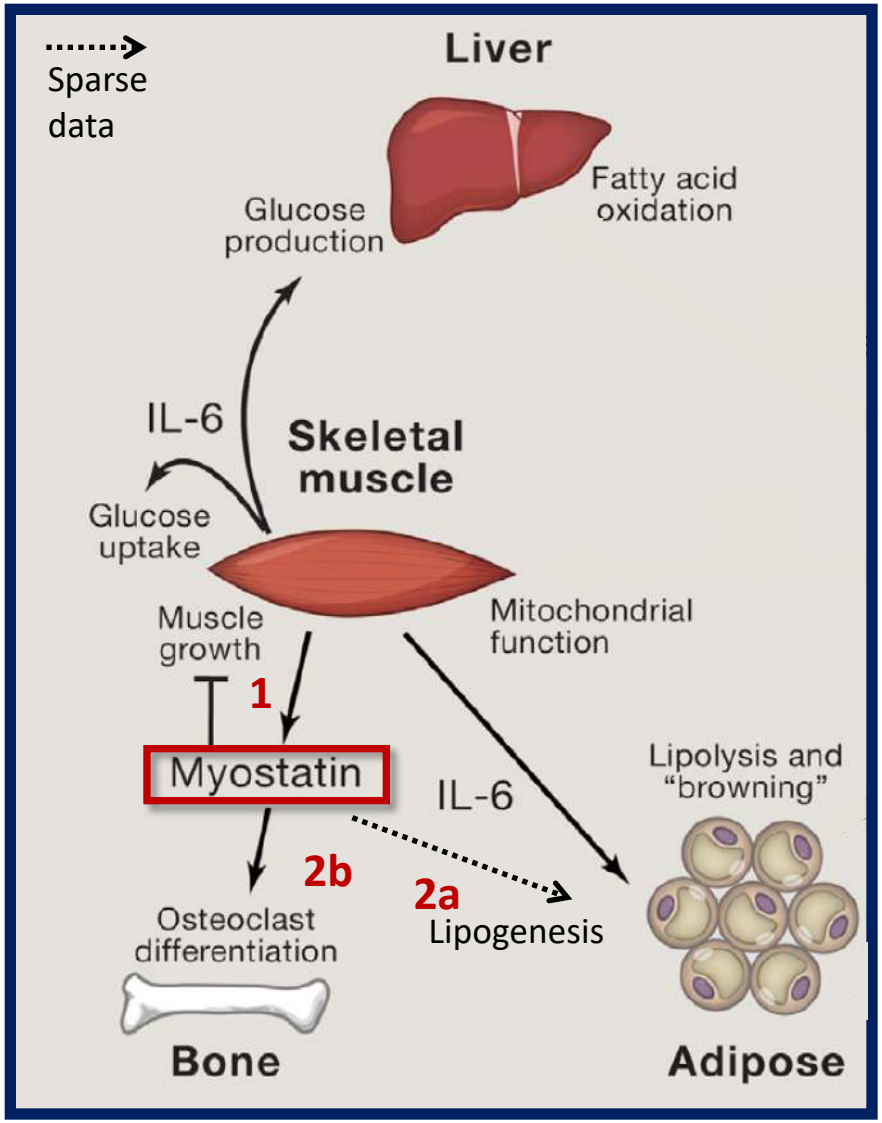

Karsenty G & Olson N, Cell 2016

MYOSTATIN

- Also known as: growth and differentiation factor (GDF-8): muscle-specific member of TGF-β superfamily
- **1) Autocrine action**: suppresses skeletal muscle growth. Loss-of-function mutations result in extreme skeletal muscle hypertrophy: increase in the number and size of myofibers during embryogenesis and post-natally, respectively
- **2) Endocrine action**: myostatin acts distally to modulate metabolism **(2a).** Mice lacking myostatin display reduced fat mass and improved insulin sensitivity. Myostatin levels are elevated in obese individuals. Myostatin can directly modulate bone remodeling by stimulating osteoclast differentiation **(2b)**

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Curr Osteoporos Rep (2013) 11:407–414
DOI 10.1007/s11914-013-0160-5

HOT TOPIC

Myostatin – The Holy Grail for Muscle, Bone, and Fat?

B. Buehring · N. Binkley

Myostatin appears to be a key factor in the integrated physiology of muscle, fat, and bone

Sparse data suggest that myostatin inhibition leads to
- muscle mass accrual
- increased lean mass
- decreased fat mass
- increased bone formation

Myostatin levels are
- increased in sarcopenia, cachexia and bed rest
- increased in obesity and decreased after weight loss from caloric restriction
- decreased after resistance training

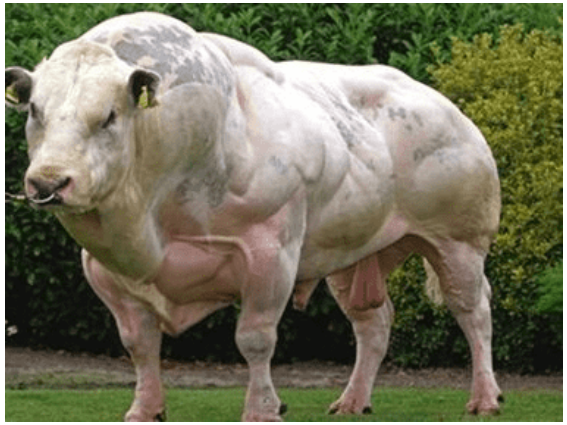
Myostatin and bone: (largely based on animal data)
- Elevated myostatin levels lead to decreased BMD
- Myostatin inhibition improved BMD

Lancet Diabetes Endocrinol. 2015 Dec;3(12):948-57.

Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial.

INTERPRETATION:
Our findings show LY treatment increases lean mass and might improve functional measures of muscle power. Although additional studies are needed to confirm these results, our data suggest LY should be tested for its potential ability to reduce the risk of falls or physical dependency in older weak fallers.

Mucche carenti in miostatina



National Geographic, "Meet the super cows".

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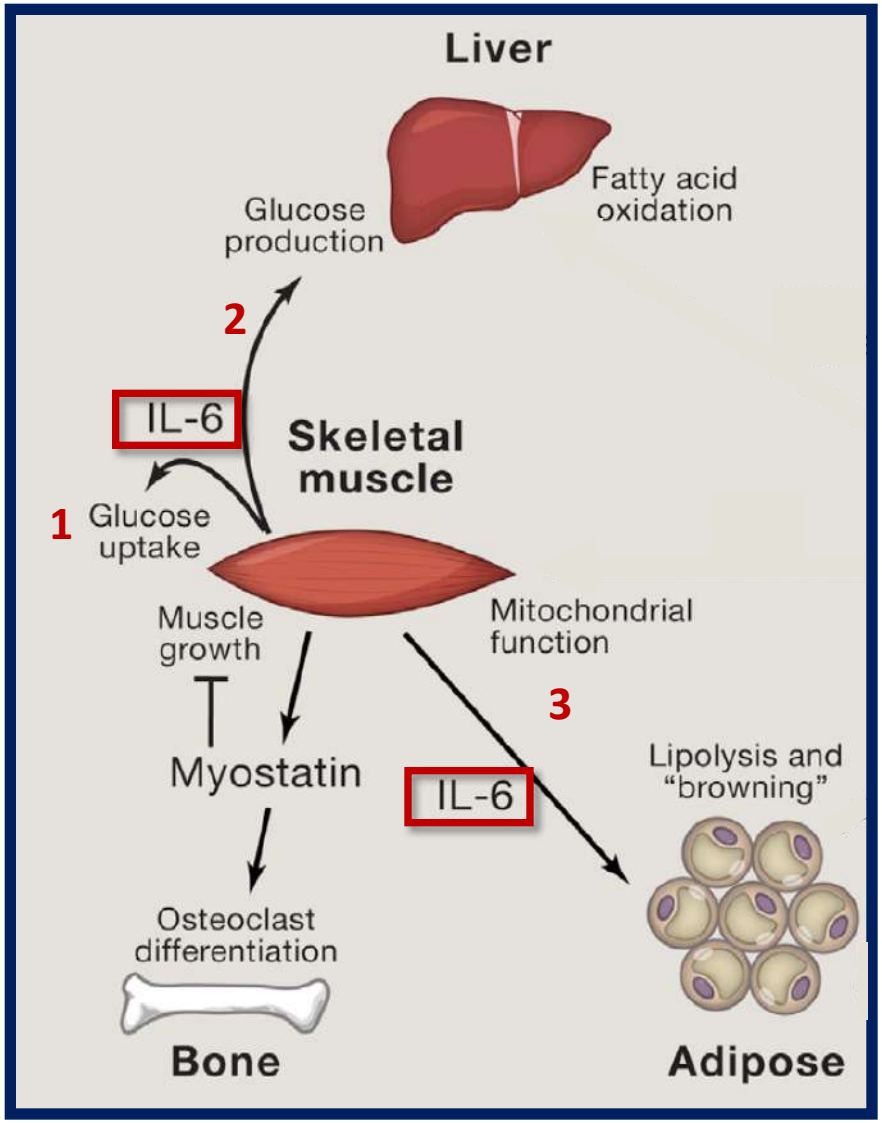
ENDOCRINE SIGNALS FROM STRIATED MUSCLES TO DISTAL TISSUES



Karsenty G & Olson N, Cell 2016

Interleukin-6

- It is a miokine markedly increased in the circulation during exercise; IL-6 is not muscle specific and, thus, it is not known which tissue is responsible for this increase
- **Autocrine action**: **1)** IL-6 acts in skeletal muscle to stimulate glucose uptake during exercise
- **Endocrine action**: **2)** IL-6 signals in the liver and in white adipose tissue, enhancing gluconeogenesis and lipolysis, respectively. **3)** IL-6 also stimulates fatty acid oxidation in adipocytes and enhances the production of anti-inflammatory cytokines

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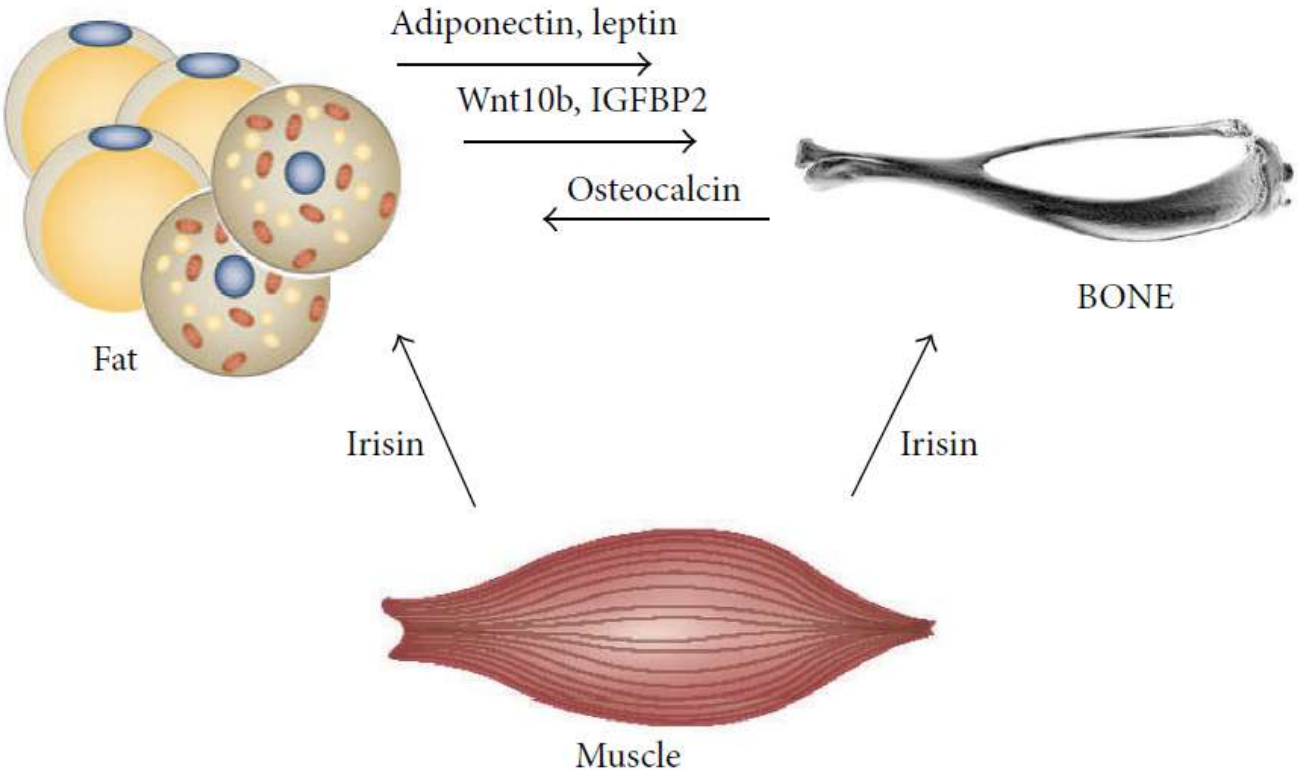
THE MUSCLE-FAT-BONE AXIS



Colaianni G et al, Int . J. Endocrinol. 2014

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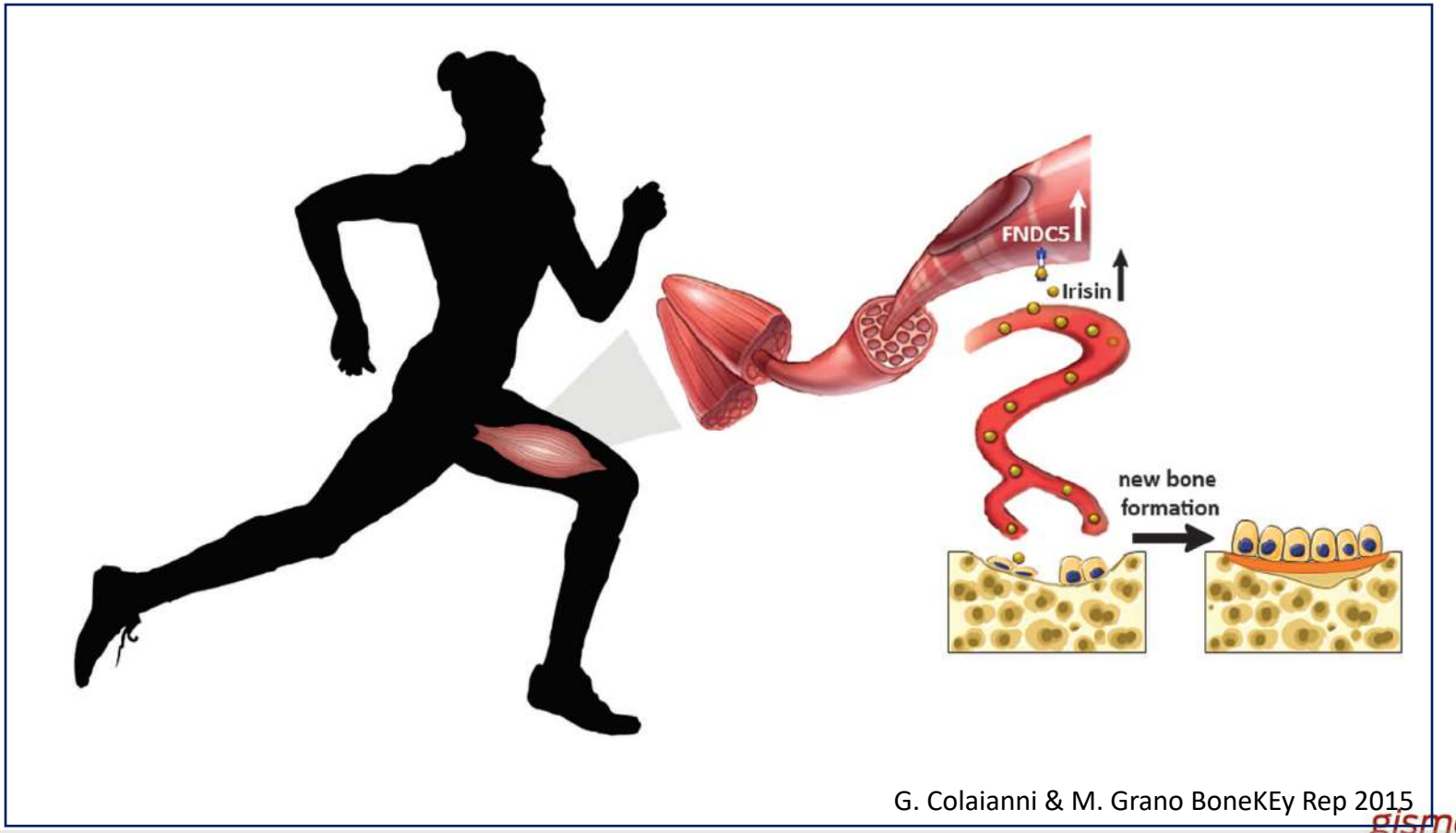
THE MYOKINE IRISIN, PRODUCED BY SKELETAL MUSCLE DURING PHYSICAL ACTIVITY, ACTS DIRECTLY ON OSTEOBLASTS BY STIMULATING THEIR DIFFERENTIATION AND ACTIVITY, THEREBY IMPROVING BONE QUALITY AND STRENGTH.



G. Colaianni & M. Grano BoneKEy Rep 2015

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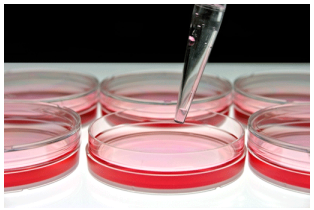
Research Article

Irisin Enhances Osteoblast Differentiation *In Vitro*

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2014, Article ID 902186, 8 pages
http://dx.doi.org/10.1155/2014/902186

Graziana Colaianni,[1] Concetta Cuscito,[1] Teresa Mongelli,[1] Angela Oranger,[1] Giorgio Mori,[2] Giacomina Brunetti,[1] Silvia Colucci,[1] Saverio Cinti,[3] and Maria Grano[1]

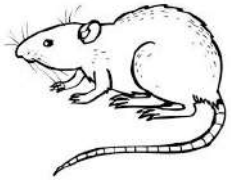


PNAS | October 20, 2015 | vol. 112 | no. 42 | E5763

CrossMark click for updates

The myokine irisin increases cortical bone mass

Graziana Colaianni[a,1], Concetta Cuscito[a,1], Teresa Mongelli[a], Paolo Pignataro[a], Cinzia Buccoliero[a], Peng Liu[b], Ping Lu[b], Loris Sartini[c], Mariasevera Di Comite[a], Giorgio Mori[d], Adriana Di Benedetto[d], Giacomina Brunetti[a], Tony Yuen[b], Li Sun[b], Janne E. Reseland[e], Silvia Colucci[a], Maria I. New[b,2], Mone Zaidi[b,2], Saverio Cinti[c], and Maria Grano[a,2]



Clinical Endocrinology (2015) 82, 615–619 doi: 10.1111/cen.12672

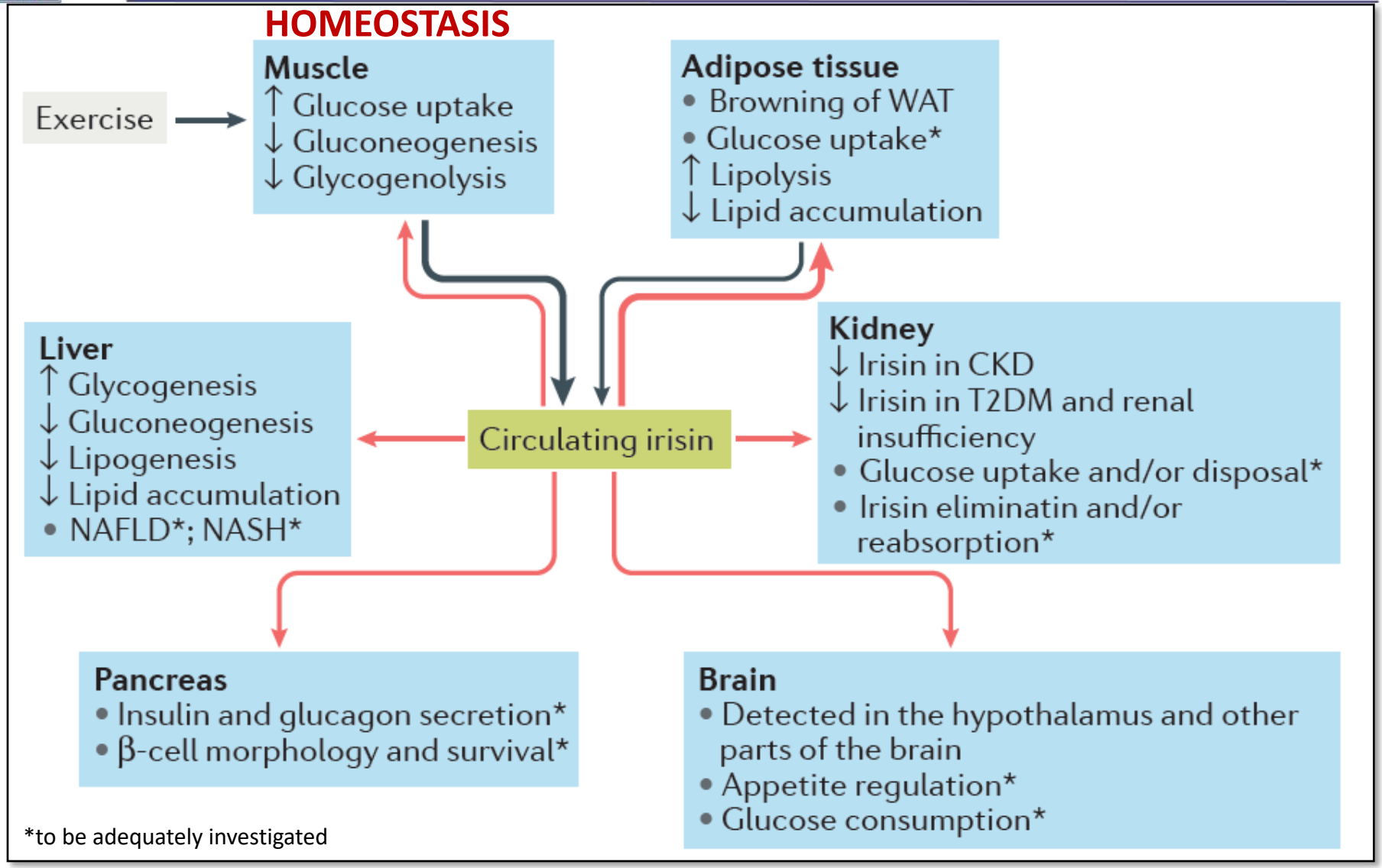
RAPID COMMUNICATION

Irisin is associated with osteoporotic fractures independently of bone mineral density, body composition or daily physical activity

Andrea Palermo*, Rocky Strollo*, Ernesto Maddaloni*, Dario Tuccinardi*, Luca D'Onofrio*, Silvia Irina Briganti*, Giuseppe Defeudis*, Mariangela De Pascalis*, Maria Concetta Lazzaro*, Georgia Colleluori*, Silvia Manfrini*, Paolo Pozzilli*,†,‡ and Nicola Napoli*

gismo.net

EFFECTS OF IRISIN ON GLUCOSE HOMEOSTASIS



Nikolaos Perakakis N et al, Nat Rev Endocrinol Metab 2017

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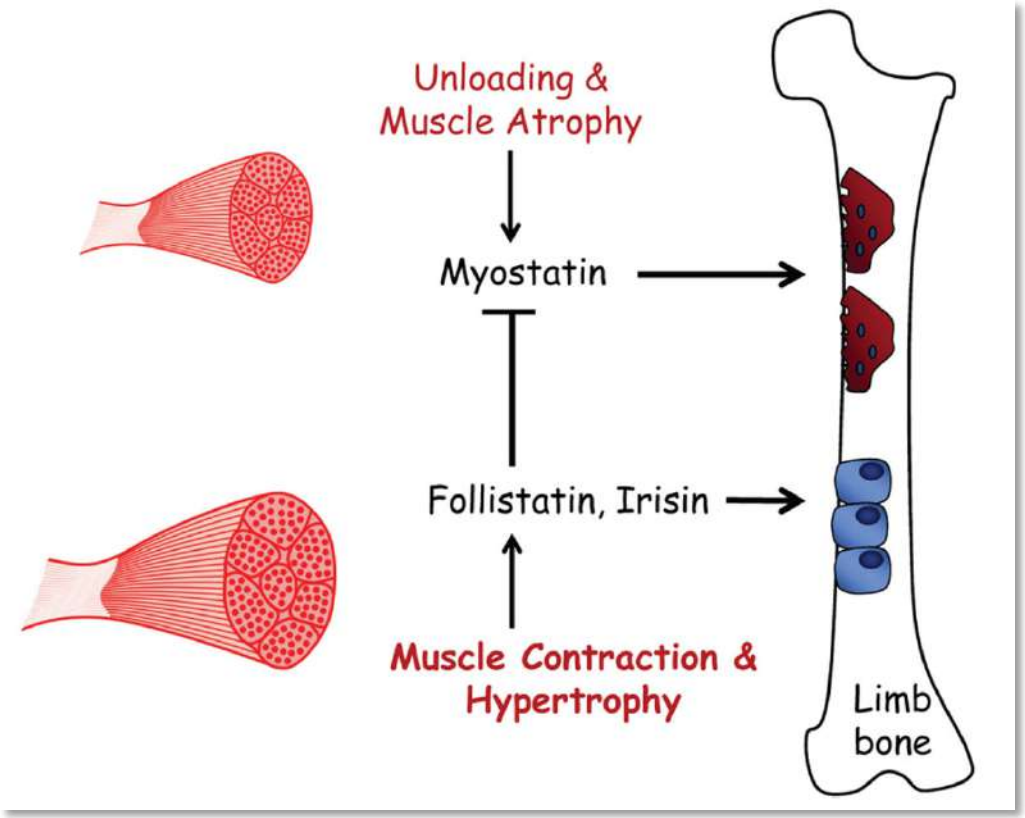
RELATIONSHIP OF MUSCLE ATROPHY AND MUSCLE HYPERTROPHY, TO MYOKINES IMPACTING BONE RESORPTION BY OSTEOCLASTS (RED) AND BONE FORMATION BY OSTEOBLASTS (BLUE).



Bettis T et al, Osteoporos Int 2018

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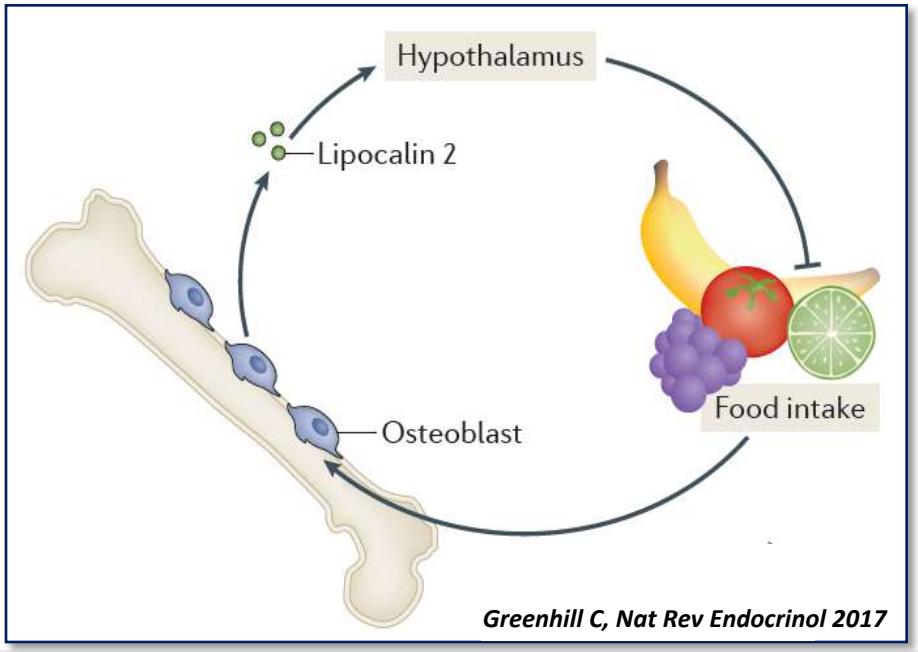
Bone has recently emerged as a pleiotropic endocrine organ that secretes at least two hormones, FGF23 and osteocalcin, which regulate kidney function and glucose homeostasis, respectively. These findings have raised the question of whether other bone-derived hormones exist and what their potential functions are. Here we identify, through molecular and genetic analyses in mice, lipocalin 2 (LCN2) as an osteoblast-enriched, secreted protein. Loss- and gain-of-function experiments in mice demonstrate that osteoblast-derived LCN2 maintains glucose homeostasis by inducing insulin secretion and improves glucose tolerance and insulin sensitivity. In addition, osteoblast-derived LCN2 inhibits food intake. LCN2 crosses the blood–brain barrier, binds to the melanocortin 4 receptor (MC4R) in the paraventricular and ventromedial neurons of the hypothalamus and activates an MC4R-dependent anorexigenic (appetite-suppressing) pathway. These results identify LCN2 as a bone-derived hormone with metabolic regulatory effects, which suppresses appetite in a MC4R-dependent manner, and show that the control of appetite is an endocrine function of bone.

Mosialou I et al, Nature 2017



Greenhill C, Nat Rev Endocrinol 2017

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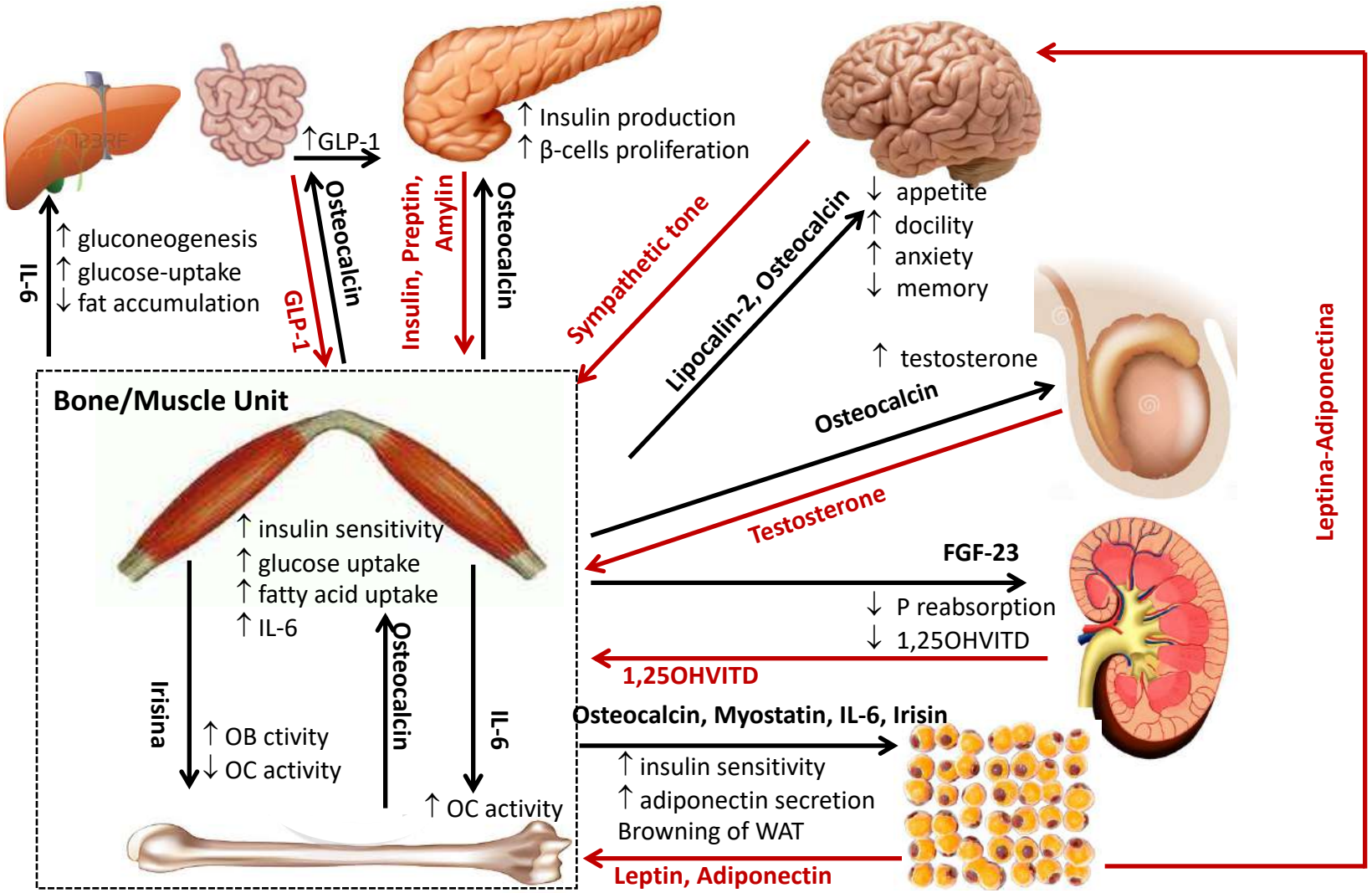
CLINICAL EFFECTS OF THE HORMONAL FUNCTION OF THE BONE-MUSCLE UNIT



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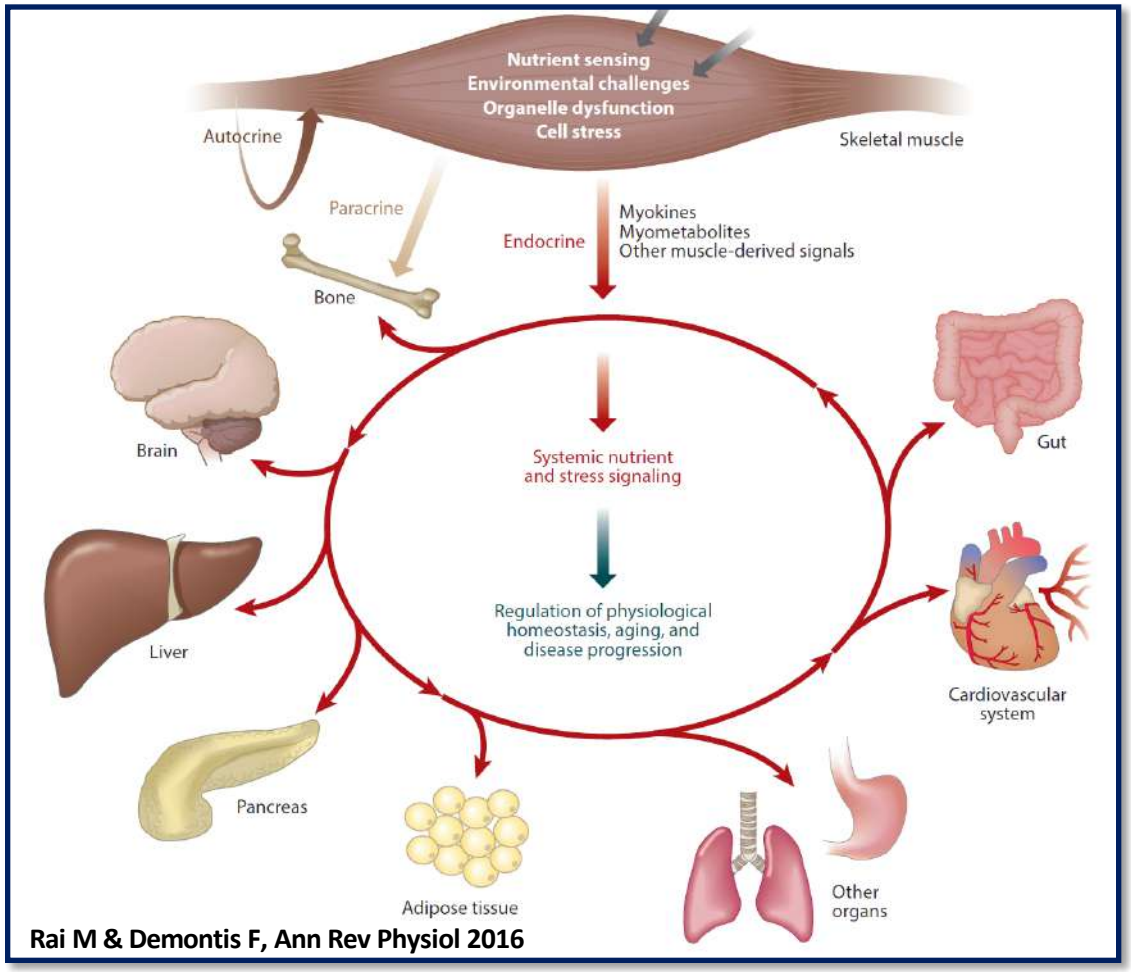
SKELETAL MUSCLE RESPONDS TO ENVIRONMENTAL AND DIETARY CHALLENGES AND TO METABOLIC DYSFUNCTION BY SECRETING MYOKINES THAT REGULATE SYSTEMIC NUTRIENT AND STRESS SIGNALING



Rai M & Demontis F, Ann Rev Physiol 2016

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GRAVITY AND MUSCLE-BONE HEALTH

- After 6 months aboard the International Space Station, nine crewmembers with an exercise prescription had a 10 to 15% reduction in calf muscle mass and a 32% decreased peak power along with a slow-to-fast fiber type transition in the gastrocnemius and soleus muscles [Trappe S et al. J Appl Physiol 2009]
- Astronauts on even short-duration spaceflight, such as 8- and 17-day mission, experienced a marked decrease in muscle volume and strength [Tesch PA et al, J Appl Physiol 2005]
- Bone mass was lost at a rate of 0.5 to 1.5% per month during a 4- to 6-month spaceflight and that proximal femur BMD was only partially recovered at 1 year after re-exposure to Earth's gravity [Lang T et al J Bone MinerlRes 2004; Lang T et al J Bone Miner Res 2006]
- Long-term bed rest can significantly decrease both muscle volume and force as well as bone mass [Bloomfield SA et al, Med Sci Sports Exerc 1997; Morgan JL et al, J Appl Physiol 2012].
- In these conditions muscle atrophy precedes the decline in bone mass and muscle loss can be recovered about six times faster than bone loss in astronauts after returning to normal gravity [Lloyd SA et al, J Bone Miner Res 2014; Keyak JH et al , Bone 2009].
- This suggests that decreased muscle-derived forces may primarily drive bone loss with unloading.

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SARCOPENIA AND BONE HEALTH

- Men with sarcopenia had significantly lower BMD and were more likely to have osteoporosis compared with those without sarcopenia in a study on middle-aged and elderly community-dwelling Europeans [Verschueren et al. Osteoporos Int 2013]

- Low muscle mass was significantly associated with higher risk of osteoporosis, even after adjusting for potential risk factors [Kim S et al, J Korean Med Sci]

- Men in the lowest quartile of relative lean appendicular mass have significantly lower section modulus of both the femoral neck and distal radius compared to men in higher quartiles of relative lean mass [Szulc P, J Bone Mineral Res 2005]

- Men in the lowest quartile of grip strength have significantly lower cortical bone area and thickness of the distal radius compared with men having higher measures of grip strength [Szulc P, J Bone Mineral Res 2005]

Distal radius cross-section:
Lowest grip strength quartile

Distal radius cross-section:
Highest grip strength quartile

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Bettis T et al, Osteoporos Int 2018

WHICH SPECIFIC TYPES OF PHYSICAL ACTIVITY ARE BEST FOR BONE?
From Adolescence to Middle Age

- The National Osteoporosis Foundation and other agencies recommend weight-bearing exercises for the prevention of osteoporosis [https://www.nof.org/patients/fracturesfall-prevention/exercisesafe-movement/osteoporosis-exercisefor-strong-bones

- These include high impact exercises such as jumping, aerobics, and running, as well as lower impact exercises such as walking and weight training. The evidence for high impact exercises is the most robust, although weight training also appears to be effective in pre-menopausal women.
- For example, repeated impact and resistive loading, i.e., plyometric training (bounding up and down, or jumping/hopping) and weight lifting, have been shown to have positive effects on bone at every age [Fuchs RK et al, J Bone Miner Res 2001; Harding A & Beck B, Sports 2017.

- A recent small clinical trial piloting high intensity resistance and impact training demonstrated significant improvements in proximal femur and lumbar spine density and geometry in postmenopausal women [Watson SL et al, J Bone Miner Res 2018].

- During adolescence, resistive exercise can increase bone strength. In middle age and post puberty, resistive training is effective at attenuating loss of bone mass and density [Harding A & Beck B, Sports 2017]

Karen L. Troy et al Int. J. Environ. Res. Public Health 2018, 15, 878

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WHICH SPECIFIC TYPES OF PHYSICAL ACTIVITY ARE BEST FOR BONE?
Aging population

- A varied exercise regimen that includes a mix of high impact and weight-bearing training, and aerobic training, may prevent senile bone loss [Gomez-Cabello A et al, Sports Med 2012;Zhao R et al, J Orthop Sports Phys Ther 2017].
- In the aging population, walking has marginal effects [Gomez-Cabello A et al, Sports Med 2012].
- Lower impact activities (cycling, yoga, and swimming, typically recommended for aging populations), are generally not osteogenic [Sherk VD et al, Clin. J. Sport Med. 2014].

- Certain yoga postures may improve monthly change of BMD only if combined with resistive weight bearing activity. [Zhao R et al, Osteoporos Int 2015]

- Osteoarthritis (OA): exercise does not negatively affect joint health, and is in fact recommended for the improvement of osteoarthritis. But, while regular high-impact exercise throughout one's lifetime does not increase the risk of OA, initiating a high-impact exercise intervention after joint degradation is present may negatively impact disease progression [Troy KL et al Int. J. Environ. Res. Public Health 2018, 15, 878]
- Other Problems: cardiovascular disease, obesity…

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Exercise Frequency and Fracture Risk in Older Adults—How Often Is Enough?

Wolfgang Kemmler[1] · Simon von Stengel[1] · Matthias Kohl[2]

Summary The minimum effective dose (MED) of ExFreq that just favorably affects BMD at the lumbar spine and femoral neck has been found to vary between 2.1 and 2.5 sessions/week. Although this MED cannot necessarily be generalized to other cohorts, we speculate that this "critical exercise frequency" might not significantly vary among adult cohorts.

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