

The colors of adipose tissue and the relationship with irisin

Los colores del tejido adiposo y la relación con la irisina

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Abstract

Excess adipose tissue is considered one of the main causes of metabolic and cardiovascular diseases. Initially, the adipose tissue was considered the main lipid and energy storage of the organism. Subsequently, it was discovered that adipose tissue had other functions such as endocrine, controlling different metabolic and immune processes. At present, different types of adipose tissue are recognized. The white adipocyte represents the main energy reserve, on the contrary, the brown adipocyte is responsible for the oxidation of lipids for thermogenesis. The beige adipocyte originates from the white adipocyte, by a process known as "browning," which leads to lipolysis and thermogenesis. The three previous types have recently joined the blue adipocyte, which has a role in liver retinoid homeostasis and the pink adipocyte that participates in lactogenesis and is present in the mammary gland of animals; its role is still unknown in humans. The newly identified hormone irisin is secreted by the skeletal muscle and promotes browning of white to beige adipose tissue, thus favoring thermogenesis. Another interesting aspect of this hormone is that it represents a connection between muscle activity and lipolysis. The above suggests that irisin may be the key in the prevention and treatment of obesity.

Keywords: Blue adipocyte. Beige adipocyte. White adipocyte. Brown adipocyte. Pink adipocyte. Irisin.

Resumen

El exceso de tejido adiposo representa una de las principales causas de las enfermedades metabólicas y cardiovasculares. Inicialmente al tejido adiposo se le consideró el almacén de lípidos y energía del organismo. Posteriormente se descubrió que presentaba otras funciones, como la endocrina, controlando diferentes procesos metabólicos e inmunitarios. Por sus características funcionales y estructurales, se reconocen varios tipos de tejido adiposo. El adipocito blanco representa la reserva energética y el adipocito marrón se encarga de la oxidación de los lípidos para la termogénesis. El adipocito beige se origina del adipocito blanco, mediante un proceso que conduce a la lipólisis y la termogénesis. A los anteriores se han sumado el adipocito azul, en el hígado, que interviene en la homeostasis de retinoides, y el adipocito rosa, que participa en la lactogénesis y se ha identificado en la glándula mamaria de animales. La irisina es una hormona secretada principalmente por el músculo esquelético, que promueve el pardeamiento del tejido adiposo blanco a beige, favoreciendo así la termogénesis.

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Otro aspecto interesante de esta hormona es que representa una conexión entre la actividad muscular y la lipólisis. Por lo anterior, la irisina puede ser una clave en la prevención y el tratamiento de la obesidad.

Palabras clave: Adipocito azul. Adipocito beige. Adipocito blanco. Adipocito marrón. Adipocito rosa. Irisina.

Introduction

Adipose tissue, which for a long time was regarded only as a depot for energy storage, fulfills other functions, such as endocrine function, by synthesizing molecules that control various actions related to the metabolism of glucose, lipids, and insulin sensitivity¹.

Adipose tissue is distributed in different regions of the body, and it can, therefore, be subcutaneous (cervical, cranial, facial, supraclavicular, gluteal, and abdominal regions), retro-orbital, paravertebral, epicardial, omental, retroperitoneal, visceral, and perigonadal². Adipose tissue localization has been observed to determine the presence of marked differences in the characteristics and functions of all different types of adipocytes. In particular, visceral adipose tissue (VAT) has gained relevance due to its association with the development of atherosclerosis, metabolic regulation, hypertension, and dyslipidemia³.

Epicardial adipose tissue has also aroused interest because it is metabolically active and for its relationship with coronary artery disease^{4,5}. Epicardial fat has been proposed to be an energy reservoir for the myocardium, and due to its metabolic activity, it also influences the production of numerous adipokines, including pro-inflammatory and pro-atherogenic cytokines such as tumor necrosis factor alpha (TNF- α), plasminogen activator inhibitor-1, interleukin-6, visfatin, leptin, omentin, and angiotensin⁶.

The colors of adipocyte

In adipose tissue classification according to its color, white adipose tissue (WAT) and brown adipose tissue (BAT) were originally considered. Subsequently, beige adipose tissue was identified, and two different types of adipocytes have recently been described, which due to their histological characteristics are called pink adipocytes and blue adipocytes^{7,8}.

It can be simply said that white adipocytes store lipids and that brown adipocytes produce heat. Both types of adipocytes share a series of genes and enzymes related to triglyceride metabolism, and for a long time, they were thought to have a common development. A few years ago, studies showed that

white and brown adipocytes did not develop from the same original cell. White adipocytes have their origin in adipoblasts. Brown adipocytes, in turn, are closer to skeletal muscle cells, with which they share the same precursor (Fig. 1). Myogenic factor 5 (Myf5) is one of the surface proteins present in this cell line and serves as a marker in identification techniques^{9,10}. PRDM16 is another molecule recently identified as a transcriptional regulator, decisive for the evolution into brown adipocytes. Peroxisome proliferator-activated receptor (PPAR γ) is a characteristic transcription factor in all adipocytes, and UCP-1 is the characteristic uncoupling protein of brown adipocytes⁹. Thus, brown adipocytes have Myf5, UCP-1, and PPAR γ as markers, and white adipocytes only have the latter.

This review has the purpose to describe the findings on different types of adipocytes and their relationship with irisin. This hormone represents a promise in the development of new anti-obesity treatments (Table 1).

WAT

WAT is the most abundant and is the body's energy reserve, which is stored in the form of triglycerides. WAT is located throughout the body and is further subdivided into visceral and subcutaneous. VAT is directly related to the risk for developing insulin resistance. Its main function is energy homeostasis, but its endocrine capacity is currently recognized, since it participates in energy metabolism regulation and pro-inflammatory cytokines expression¹⁰.

Lipid absorption in WAT is mediated by the lipase lipoprotein, which is bound to vascular endothelium through heparin sulfate proteoglycans, with active sites located on the luminal surface of blood vessels, which allows triglycerides to be hydrolyzed to be mobilized and used in cell storage¹¹. White adipocyte exhibits a large lipid droplet, which covers most of its cytoplasm, and its nucleus is located at the cell periphery. Lipids are free within adipocytes and correspond to triglyceride deposits¹². Excessive lipid accumulation in WAT adipocytes is associated with higher cardiovascular and metabolic risk, related to

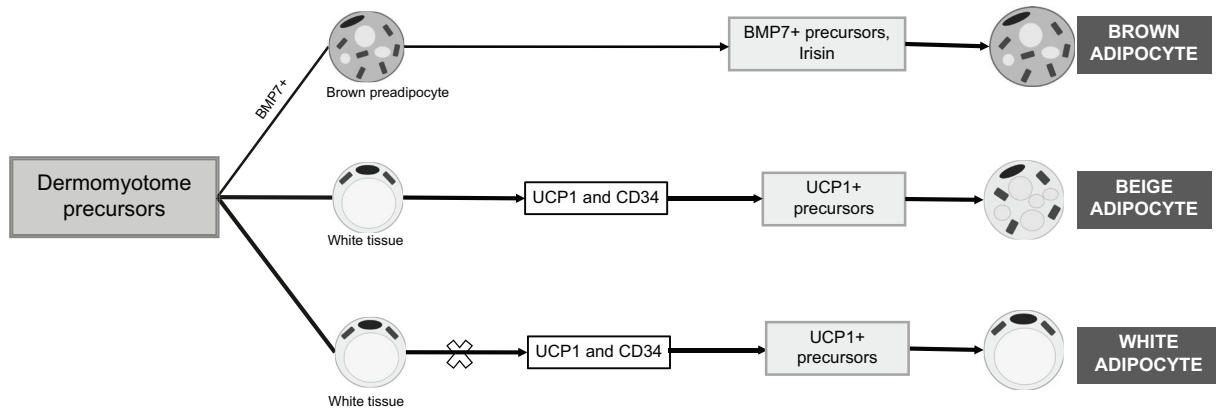


Figure 1. Differentiation starts in dermomyotome; brown adipocytes originate from the subpopulation of brown preadipocytes, with positive BMP7 and irisin markers. White adipocyte precursors that do not express BMP7 and UCP1 become white adipocytes. On the other hand, white preadipocytes that express UCP1 and some other markers (ZIC1negative, Cd137 and TMEM26 positive) are transformed into beige adipocytes.

Table 1. Characteristics of white, brown, beige, blue, and pink adipocytes

	White	Brown	Beige	Blue	Pink
Localization	Inguinal, mesenteric (retroperitoneal, perigonadal, omental)	Interscapular, perirenal, axillary and paravertebral	White adipose tissue	Hepatic, space of Disse, underlying endothelial cells	Mammary gland
Morphology	Unilocular, with large lipid droplets	Multilocular, with small lipid droplets	Multiple lipid vacuoles	Multilocular, containing vitamin A	Multilocular
Function	Energy storage in the form of triglycerides	Heat production	Adaptive thermogenesis	Extracellular matrix homeostasis	Milk secretion
Generation of mitochondria	+	+++	++ post-stimulation	*	*
Vascularization/capillaries	Low	Abundant	Cold stimulation increases angiogenesis	*	*
UCP-1	Almost undetectable	+++	Post-stimulation (abundant)	*	*
Adrenergic receptors	β_3 ++, α_2 +	β_3 +++	β_3/α_2	*	*
Relationship with obesity and insulin resistance	Positive effect	Negative	Negative	Negative effect on lipid homeostasis and insulin resistance	
Activators	Fat-rich diet	Thyroid hormones, thiazolidinediones, FGF21, BMP7, BMP8B, natriuretic peptide	Irisin, FGF21, natriuretic peptide, catecholamines, (β -agonists) thiazolidinediones	Parenchymal cell lesion, oxidative stress	*

BMP: bone morphogenetic protein; FGF21: fibroblast growth factor 21; UCP-1: uncoupling protein 1. * Controversial or unknown data.

the release of pro-inflammatory cytokines with secretory activity, such as TNF- α , interleukin-8, and C-reactive protein¹³.

Compared to subcutaneous WAT, VAT shows higher infiltration of inflammatory and immune cells, which are a source of different inflammatory cytokines¹². VAT excess is associated with higher cardiovascular risk, atherosclerosis, hypertension, and

type 2 diabetes mellitus (DM) than subcutaneous adipose tissue¹³. Another difference from visceral WAT is its high sensitivity to lipolytic stimuli that increase free fatty acids in portal circulation and lead to higher insulin resistance. Compared to subcutaneous WAT, visceral adipocytes show an increase in glucocorticoid receptors and an increase in lipoprotein lipase activity¹².

BAT

BAT, in contrast to WAT, is made up of smaller adipocytes constituted of multiple small lipid droplets (multilocular). Brown fat adipocytes originate from embryonic mesoderm precursor cells. Histologically, other features that distinguish brown from white tissue are vascularization and innervation. Functionally, BAT main characteristic is lipolysis and energy release. Thus, individuals with smaller BAT deposits have a higher susceptibility to accumulate WAT and increase their body weight, and higher risk of cardiovascular diseases¹⁴.

Lipid oxidation in brown tissue for producing heat is due to the presence of large numbers of mitochondria and uncoupling protein (UCP1). This protein favors the release of energy¹⁵. This function is especially important in the newborn for preventing hypothermia. BAT is more abundant in the newborn and is distributed in the interscapular, cervical, supraclavicular, paravertebral, para-aortic, and adrenal regions^{15,16}. As age advances, BAT loses mitochondria and can be transformed into white fat, and is found in less quantity¹⁶.

In the central nervous system, catecholamines and orexin are produced, which are considered powerful activators of the development of brown fat and of thermogenic function¹⁴. Activated macrophages residing in adipose tissue also secrete some molecules that stimulate thermogenesis¹⁶.

The balance between white and BAT can be modified in response to different factors, such as cold, heat, obesity, and age; therefore, individuals with less BAT have more susceptibility to accumulate WAT and higher risk of metabolic and cardiovascular diseases¹⁷.

Beige or *brite* adipose tissue

Adipocytes with brown adipocyte characteristics have been observed to be likely to exist in WAT, which has led to the concept of beige or *brite* adipocyte (the latter term derived from the words brown and white). These adipocytes have similarity to brown adipocytes and thermogenic properties.

Beige adipocytes were discovered in an animal experiment in which, when animals were chronically exposed to cold, they were observed to transform their white fat into brown, suggesting the need to generate thermal energy. In another experiment, also in animals on a hypercaloric diet, some BAT deposits were

shown to turn into white fat, which suggested that BAT had the ability to adapt for storing energy^{14,17}.

The above experiments suggested for the 1st time the process of adipocyte trans-differentiation, that is, white adipocyte precursor cells may exist and, depending on the stimulus they are subjected to, they may transform into beige adipocytes (Fig. 1). The presence of beige adipocytes within WAT has been demonstrated in different species and is under the control of different factors, such as chronic exposure to cold, adrenergic agonists and PPAR γ agonists, including thiazolidinediones^{18,19}.

The exact mechanisms of white to beige adipocyte conversion have not been identified. Although their structure and function are similar, beige adipocytes, present in islets within WAT, do not have the same origin as conventional brown tissue. In this regard, there are three hypotheses: in the first one, beige adipocytes would originate from adipoblasts through an alternative cellular pathway; in the second, it would originate from an alternative differentiation of white preadipocytes; and the third and most accepted hypothesis is that beige adipocytes originate from mature white adipocytes by direct differentiation (trans-differentiation)²⁰.

The production of adenosine triphosphate (ATP) in beige adipocytes is replaced by the generation of heat. That is, oxidation of fats and carbohydrates, which normally leads to ATP formation at the end of the respiratory chain, causes heat release instead. This ATP production dissociation is called "uncoupling," and it occurs thanks to a protein called thermogenin or more commonly UCP-I. This uncoupling protein, located at inner mitochondrial membrane, prevents membrane transport of protons and hinders ATP synthase function; this way, the energy accumulated by the transfer of electrons in respiratory chain complexes is released in the form of heat^{9,17}.

A recently identified hormone, irisin, synthesized by muscle tissue, has the ability to confer certain properties that are characteristic of brown fat to white fat deposits, specifically thermogenesis stimulation. Other molecules, such as transforming growth factor-beta and natriuretic peptide, also stimulate thermogenesis and BAT development through the browning of white fat. From the liver, fibroblast growth factor 21 is also a mediator of this trans-differentiation process (Fig. 2).

Pink adipocyte

Pink adipocytes receive their name for the pink color they acquire with hematoxylin-eosin

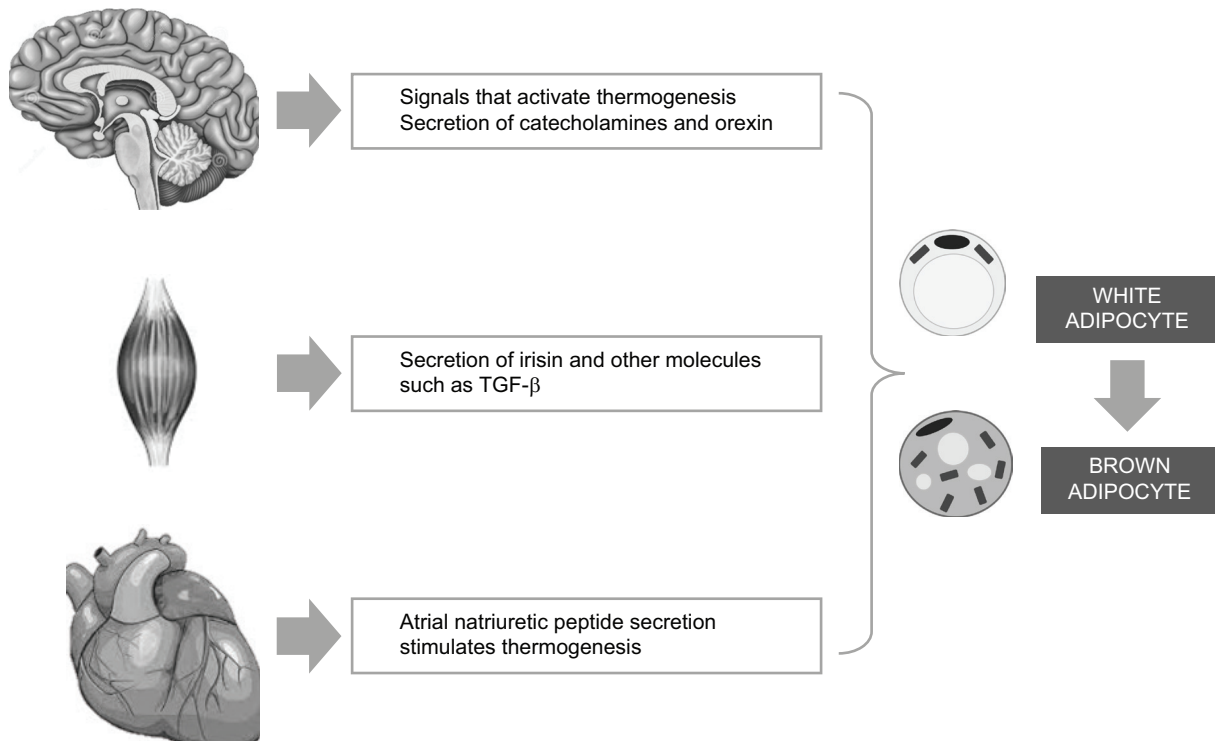


Figure 2. Molecular differences determine the transformation of white to brown adipocytes and, consequently, thermogenesis increases. Catecholamines and orexin are produced in the nervous system, but there are also other molecules secreted in other tissues and organs, such as skeletal muscle, the heart, and liver, which are involved in trans-differentiation. TGF- β : transforming growth factor-beta.

staining⁷. Pink adipocytes were identified in subcutaneous adipose tissue of gestating and lactating mice. Pink adipocytes correspond to mammary gland alveolar cells, which store a large amount of lipids and their main function is milk production and secretion^{21,22}.

During pregnancy and breastfeeding, subcutaneous adipose tissue deposits are replaced by alveolar cells with abundant lipids. Pink cells probably originate from a process of trans-differentiation from subcutaneous WAT, and under hormonal control, they progressively acquire epithelial characteristics. The trans-differentiation process is probably reversible in the mouse mammary gland, that is, the epithelium can be differentiated into an adipocyte and adipocytes into epithelial cells.

This process has not yet been identified in women, but knowledge on the trans-differentiation mechanisms could help understand aspects related to the appearance of breast tumors²². Another interesting observation is that pink adipocytes also express adipokines such as leptin and perilipin A, which probably participate in the prevention of obesity in mouse pups²¹.

Blue adipocyte

Cells with a stellate appearance that characteristically store lipids, known as lipocytes or stellate cells, are found in the liver. These cells are also called blue adipocytes, due to the color their lipid vesicles acquire by autofluorescence²³. They are found in the perisinusoidal space between hepatocytes and endothelial cells. Blue adipocytes play a key role in retinoid homeostasis and extracellular matrix remodeling²⁴. Blue adipocytes, at their quiescent or inactive state, have a large number of cytoplasmic fat vesicles that constitute the main storing place of Vitamin A in the body.

As a consequence of various stimuli, such as chronic inflammation, alcohol consumption, or infections, among others, blue adipocytes transition into a second activation state, losing their fatty vesicles and undergoing a process of trans-differentiation into proliferative cells and myofibroblasts. During this activation stage, blue adipocytes express different adipokines, such as leptin, resistin, chimerin, adiponectin and interleukins, among others, which affect lipid metabolism and increase insulin resistance and immune response. Fibrinogenesis, and eventually liver fibrosis, subsequently ensues²⁵.

It is controversial whether blue cells are part of adipose tissue; however, due to some characteristics they exhibit, such as fat storage, adipokine production, and participation in lipid metabolism, the blue adipocyte designation seems appropriate.

Irisin

Irisin is a recently identified molecule and has drawn attention because it is secreted by skeletal muscle and may be a signal of direct communication with adipose tissue. It is due to this characteristic that it has received its name, similar to that of Greek goddess Iris, who communicated Olympic gods with mortals.

In 2012, Boström et al.²⁶ identified irisin for the 1st time, observing in murine models that its elevation increased energy expenditure, controlled diet-induced weight gain, and improved insulin resistance.

An important fact is that irisin has the ability to trans-differentiate white to beige adipocytes, by promoting UCP-1 expression. Irisin transforms white fat by activating mitogen-activated protein kinase (MAPK) p38. MAPKp38 activation is essential for PGC1 α (PPAR γ coactivator α) expression^{27,28}. The trans-differentiation process apparently does not occur in all adipocytes. In experimental models, VAT adipocytes have been observed not to generate p38 when stimulated with irisin, which suggests that trans-differentiation does not occur in this visceral tissue; however, irisin, by other mechanisms not yet fully understood, causes a decrease in the production of pro-inflammatory cytokines²⁹.

Physical exercise stimulates PGC α , which, in turn, stimulates the expression of FNDC5 (fibronectin type III domain-containing protein 5), from which irisin is released²⁸. Once secreted, it is distributed by the bloodstream and acts on different structures, such as adipose tissue, cardiac muscle, the liver, brain, bone, pancreas, kidney, and ovary. Thus, one of the benefits of exercise is the release of myosins, including irisin, which, in turn, has the effect of increasing energy expenditure and fat oxidation. Different clinical trials have shown that there is an increase in irisin concentration after exercise³⁰. Individuals with higher physical activity show an increase in irisin circulating concentration and a slight decrease in insulin resistance, in comparison with physically inactive individuals^{27,30}.

Irisin improves insulin sensitivity by increasing the response of its receptor in muscle tissue, favors

hepatic glucose and lipid metabolism, and promotes the function of pancreatic β cells³¹. In clinical trials, an association between decreased circulating irisin and insulin resistance has been observed³². Other studies have also shown a reduction in irisin concentration in patients with DM, and others have found a negative correlation with fasting glucose^{32,33}. Similarly, a significant decrease in irisin levels has been observed in patients with newly diagnosed DM³⁴.

In pregnant women, irisin is also secreted in the placenta, and its concentration increases during gestation. Studies in women with gestational DM are scarce and with controversial data, but irisin has been reported to be decreased in comparison with healthy pregnant women, and it has been proposed as a marker for gestational DM³⁵.

Another aspect of this hormone is its relationship with blood pressure. In animal models, peripheral administration of irisin decreases vasoconstriction by stimulating nitric oxide production and activating the AMPK pathway³⁶. In humans, studies have shown a negative correlation between irisin and blood pressure (systolic and diastolic) in women with preeclampsia³⁶. Further studies are required in this area in order to clarify the relationship between irisin and high blood pressure.

The effect of irisin on body weight observed in mice has also been found in clinical trials. In patients with obesity, irisin is decreased and negatively associated with waist circumference³². In patients with obstructive sleep apnea, regardless of body mass index (BMI), irisin is associated with apnea³⁷, which is why irisin has been proposed to likely be a messenger molecule between an axis formed by muscle, adipose, and cerebral tissues³⁷. Moreover, other investigations in experimental models have shown that irisin influences hippocampal neurogenesis and neural differentiation³⁷.

Information on the topic suggests that irisin has numerous potential benefits on weight, metabolism, and cardiovascular risk. However, paradoxically, in some studies, irisin concentration in obese patients has been observed to be directly associated with some adiposity indices, such as BMI, waist circumference, total amount of fat, and insulin resistance^{33,38,39}. In this regard, two hypotheses have been proposed. The first one is that, after muscle, adipose tissue is the second site of irisin production, and thus, the rate of irisin secretion in muscle/adipose tissue could vary in situations such as obesity⁴⁰. Another hypothesis to explain the discrepancy

in the results between slender and obese people is that irisin concentration in the latter could be a compensatory mechanism for increasing energy expenditure, improving insulin sensitivity, and maintaining metabolic homeostasis⁴¹. One study described a positive effect of irisin on pancreatic β cells regeneration through betatrophin action, which could explain insulin resistance increase in non-diabetic patients with obesity⁴². Similarly, an increase in irisin concentration has been observed in women with morbid obesity, with a positive association between its concentration and BMI⁴³. Thus, irisin resistance in patients with obesity probably corresponds to a phenomenon similar to that of leptin and insulin resistance^{40,44}.

Irisin actions in energy metabolism regulation and thermogenesis and insulin sensitivity increase might have an impact on health and metabolic diseases.

Conclusion

Adipose tissue still has many secrets that need to be clarified, and the knowledge accumulated in recent years has to be disseminated. One of the main reasons is because an excess of this adipose tissue, obesity, represents a critical health problem.

Irisin is a communication bridge between muscle and adipose tissue, and its action is noteworthy in the trans-differentiation of white to beige adipocytes, thus increasing their thermogenic capacity. That is, in simple terms, irisin can transform “bad” fat into “good” fat. However, it is necessary for some aspects of its action and the differences that occur between different clinical conditions to be clarified.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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