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Review article

Secreted protein acidic and rich in cysteine and bioenergetics: Extracellular matrix, adipocytes remodeling and skeletal muscle metabolism

Abdelaziz Ghanemi[a,b], Aicha Melouane[a,b], Mayumi Yoshioka[a], Jonny St-Amand[a,b,*]

[a] Functional Genomics Laboratory, CREMI, Québec Genome Center, CHUL-CHU de Québec Research Center, Québec, Québec G1V 4G2, Canada
[b] Department of Molecular Medicine, Faculty of Medicine, Laval University, Québec, Québec G1V 0A6, Canada

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ABSTRACT

The extracellular matrix (ECM) remodeling plays important roles in both adipocytes shape/expansion remodeling and the skeletal muscle (SM) metabolism. Secreted protein acidic and rich in cysteine (SPARC) is expressed in divers tissues including adipose tissue (AT) and SM where it impacts a variety of remodeling as well as metabolic functions. SPARC, also known as osteonectin or BM-40, is a glycoprotein associated with the ECM.

Numerous researches attempted to elucidate the implications of SPARC in these two key metabolic tissues under different conditions. Whereas SPARC deficiency tends to shape the remodeling of the adipocytes and the fat distribution, this deficiency decreases SM metabolic properties. On the other hand, SPARC seems to be an enhancer of the metabolism and a mediator of the exercise-induced adaptation in the SM and as well as an adipogenesis inhibitor.

Some findings about the SPARC effects on AT and SM seem "contradictory" in terms of tissue development and energy profile therefore highlighting the mechanistic role of SPARC in both is a priority. Yet, within this review, we expose selected researches and compare the results. We conclude with explanations to "reconcile" the different observations, hypothesize the feedback and regulatory character of SPARC and put its roles within the energetic and structural maps of both adipocytes and myocytes in homeostasis and in situations such as obesity or exercise.

These properties explain the modifications and the remodeling seen in AT and SM undergoing adaptive changes (obesity, exercise, etc.) and represent a starting point for precise therapeutic targeting of SPARC-related pathways is conditions such as obesity, sarcopenia and diabetes.

1. Secreted protein acidic and rich in cysteine (SPARC): from biological remodeling to energy balance

Disorders in energy homeostasis and metabolic biofunctions represent the origins of divers health problems and diseases such as obesity and diabetes. Obesity can result from the accumulated effects of minor imbalances between energy intake and expenditure (Jequier, 2002). Overweight and obesity are defined by the World Health Organization as abnormal or excessive fat accumulation that presents a risk factor for diabetes, cardiovascular disease, dyslipidemia, cancer and other chronic diseases (Health topics, 2019; Ghanemi and St-Amand, 2018; Kilov and G, 2018). These energy imbalances are the consequence of the modern unhealthy diet characterized by an increased intake of food, mainly with high caloric density, combined to a sedentary lifestyle, in addition to factors such as psychological impacts and sleep shortage (Ghanemi et al., 2018a). Creating a deficiency in the energy balance is the basis of anti-obesity approaches. It is achieved either via a caloric restriction (limit the food intake), exercise (increase energy expenditure) or the combination of both.

Studying the dynamic expression of genes related to factors involved in obesity development and therapies such as diet, mainly high-fat (HF) diet (Yoshioka et al., 2008; Mucunguzi et al., 2017; Ghanemi et al., 2018b) and exercise (Nishida et al., 2010; St-Amand et al., 2012) would allow a better understanding of the underlying mechanisms and lead to the identification of new molecular therapeutic targets in key tissues such as adipose tissue (AT), skeletal muscle (SM) and digestive mucosa. Functional genomics represents one of the strong tools for such genes characterization and allows exploring genes expression changes/adaptations under dynamic conditions including exercise. For instance, gene-encoding SPARC was characterized as an exercise-induced gene (Riedl et al., 2010). This represents one of the key steps toward understanding underlying molecular mechanisms implicated in SM

* Corresponding author at: Functional Genomics Laboratory, CREMI, CHU de Québec Research Center, 2705 Boul. Laurier, Québec, Québec, G1V4G2 Canada.
E-mail address: jonny.st-amand@crchudequebec.ulaval.ca (J. St-Amand).

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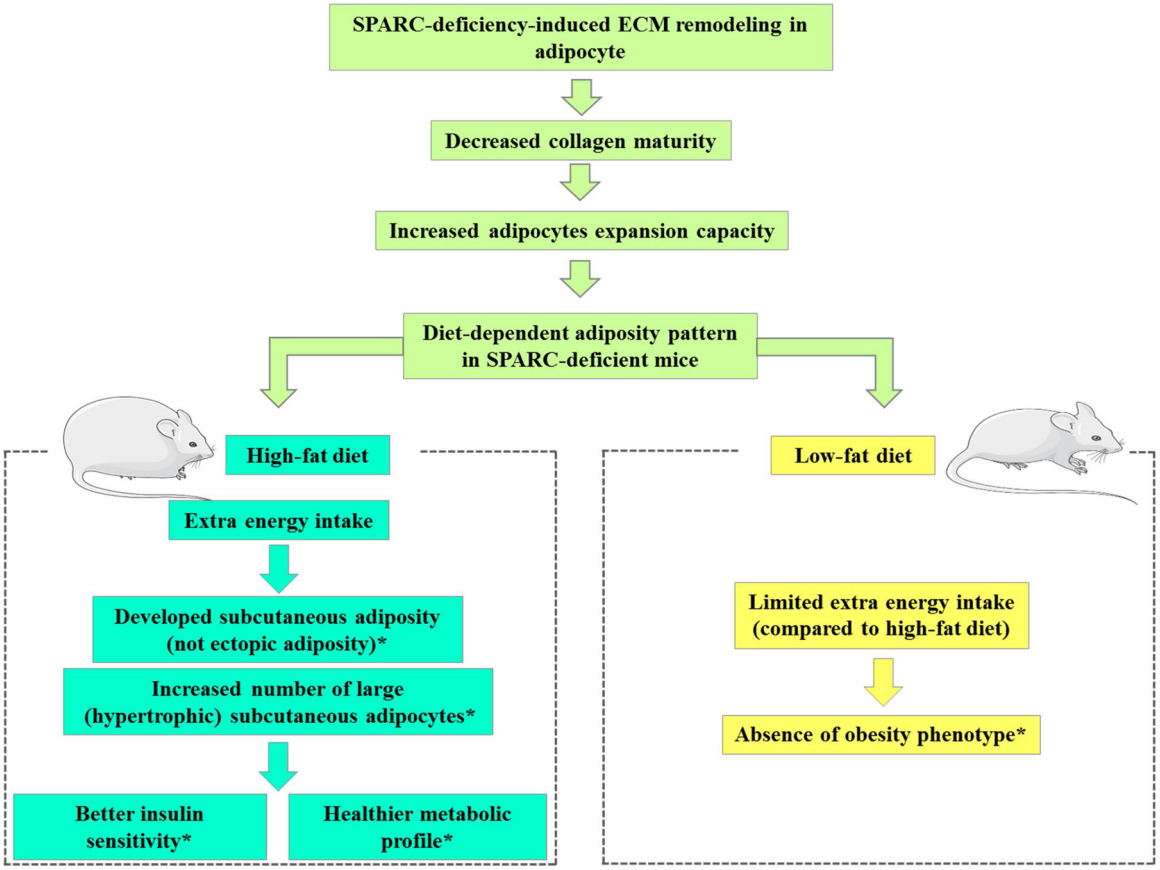

Fig. 1. The difference in ECM between subcutaneous and other adipocytes localizations makes that only an extra energy intake "reveals" a significant difference in adiposity development (development ability) pattern between different localizations.
*: Compared to WT mice.
Abbreviations: **ECM**: Extracellular matrix remodeling; **SPARC**: Secreted protein acidic and rich in cysteine; **WT**: Wild type.

adaptation and adiposity modification during exercise and identify potential therapeutic targets not only for obesity but also for diabetes, sarcopenia and related metabolic disorders.

SPARC (known as osteonectin or BM-40) is a 32-kDa glycoprotein expressed mainly when tissues undergo changes such as tissue renewal, remodeling and repair (Termine et al., 1981). It is made of three domains (Lane and Sage, 1994; Bradshaw and Sage, 2001; Brekken and Sage, 2000) and is encoded by the gene SPARC in the chromosomal site at 5q31-q33 in human (Swaroop et al., 1988) and localized to the central region of chromosome 11 in mouse (Mason et al., 1986a). SPARC is a calcium binding matricellular glycoprotein secreted by several types of cells in many organisms, and it is associated with extracellular matrix (ECM) organization and remodeling, growth, cellular differentiation, wound repair and tissue response to injury (Bradshaw and Sage, 2001; Tai and Tang, 2008; Basu et al., 2001; Rosset and Bradshaw, 2016). SPARC binds to matrix proteins and controls cellular interaction with the ECM (Brekken and Sage, 2000). ECM represents a network of macromolecules including fibronectin, collagens and glycosaminoglycans that control a variety of biological functions such as signals transduction and allow cellular adhesion to form tissues and organs (Theocharis et al., 2016). This implication of SPARC in ECM functions suggest that alterations, including the deficiency and over expression, of SPARC would have an impact on the ECM remodeling, thus, influences how the cells receive surrounding signals and respond to them and also impact the divers cellular functions and properties such as cell shape and polarity, growth, tissue expansion pattern and energy metabolism such as those reported in studies linking SPARC and cancer (Naczki et al., 2018; Said et al., 2007; Neuzillet et al., 2013).

It is worth mentioning that in spite of these important functions modulated by SPARC, SPARC-deficient mice have similar growth, fertility, and viability compared to wild-type (WT) mice (Norose et al., 1998). This allows reproducing, observing and, most importantly, studying this genetically modified model and learn more about this gene and its encoded protein. In addition, results obtained from studying SPARC in mice could be reasonably extrapolated to humans due the high homology between mouse and human SPARC (Norose et al., 1998). Herein, we focus on how changes in SPARC expression impact two keys metabolic tissues, AT and SM, mainly through the ECM remodeling and the metabolic changes involving the mitochondria. These two tissues represent the main site of energy storages and energy expenditure, respectively and have the highest importance within obesity and metabolic homeostasis researches.

2. SPARC and adipocytes: ECM impacts adiposity distribution

Development of obesity is known to be under the influence of diver factors such as genetics, environment (including diet), exercise, sleep shortage and psychology (Ghanemi et al., 2018a). Obesity is considered as a status in which cells undergo selected modification in order to adapt to the new energetic status. Within this context, describing the ECM remodeling implication in both adipocytes development and fat distribution represents the key to understand the role of SPARC in obesity development. AT is the main tissue of energy storage and the key tissue in obesity pathogenesis (Ghanemi et al., 2018a).

Different studies and observations linking gene-encoding SPARC to adiposity and adipogenesis have been reported in the literature. However, not all results have similar conclusions. These differences seen among the effects of SPARC deficiency could be due to different

factors such as the mice age, genetic background, investigated tissues, their localization and diet (type and composition). For instance, the work of (Bradshaw et al. (2003a)) have reported SPARC-deficient mice with increased fat deposition in epididymal and dermal (with increased-diameter adipocytes) but not in major organs including liver, lung, and kidney with a HF diet but not with a low-fat (LF) diet although the food intake was similar (Nie et al., 2011). This suggests that a reduced energy expenditure is, at least in part, beyond this enhanced HF diet-induced weight gain. Especially that when handled, SPARC-deficient mice have been reported as passive and with reduced physical activity (lower mobility-related energy expenditure) compared to WT mice (Norose et al., 1998). Importantly, the differences in the ECM between subcutaneous AT of WT and SPARC-deficient mice could be explained by the adaptive properties of the adipocytes ECM (Mori et al., 2014; Lin and Kang, 2016) and indicate why SPARC-deficient mice fed with HF-diet had more fat deposit within the dermal AT compared to WT. Indeed, since SPARC is an important component of the ECM, its deficiency reduces the ECM (mesangial cells) (Taneda et al., 2003) and would reduce the "rigidity" of the ECM (SPARC-deficiency-induced ECM remodeling) and thus, increases the expansion ability of the adipocytes (Fig. 1) especially in the subcutaneous AT in which SPARC expression is predominant compared to visceral AT (Kos et al., 2009). Therefore, the subcutaneous AT would be more affected by SPARC deficiency and develop a greater ability to expand and store fat compared to the visceral AT (whereas the opposite is seen WT mice).

Obesity development is not only about the fat tissue percentage, but also about the ability of adipocyte to expand both in number (hyperplasia) and size (hypertrophy) (Ghanemi et al., 2018a). Thus, histological studies of adipocytes remain an essential element. Bradshaw et al. showed that although SPARC-deficient mice had increased fat accumulation and total number of adipocytes in epididymal pads, those adipocytes were bigger and thus the number of fat cells per gram of epididymal pads tissue was lower (Bradshaw et al., 2003b). These suggest that this tissue expansion resulted from the increase of adipocyte size, likely due to the decrease of collagen I (Francki et al., 1999) in the same reported tissue (Bradshaw et al., 2003a). This is similar to what was seen in the dermis of SPARC-deficient mice of another study as well (Bradshaw et al., 2002) and which is also similar to what has been reported by Mansergh et al. (increased in bone marrow adipocyte size and not number in SPARC-deficient mice at the age of 4 months) (Mansergh et al., 2007). Therefore, this indicates that in this situation, SPARC-deficient mice have an increased size of adipocytes rather than increased differentiation of preadipocytes into adipocytes in the epididymal AT (hypertrophic fat accumulation). Importantly, the fact that in SPARC-deficient mice the increased adiposity was observed in epididymal and subdermal AT but not in liver, lung or kidney (Bradshaw et al., 2003a), further supports that this enhanced adiposity affects more subcutaneous AT rather than the ectopic localizations. Interestingly, the increased adipocytes size rather than preadipocytes differentiation into adipocytes reported in SPARC-deficient mice further emphasize the importance of SPARC. This highlights SPARC in cell differentiation as a macromolecule expressed specifically when tissues undergo changes which explains why the SPARC-deficient adipocytes have limited differentiation. Therefore, points once again obesity-developing status as a biological change requiring cell differentiation and ECM remodeling.

The ECM remodeling phenomenon, involving different enzymes and factors, is not limited to AT. It has been reported in different tissues such as cardiac tissue (McCurdy et al., 2010), lung (Tomos et al., 2017), brain (Miyata and Kitagawa, 2017), peripheral neurons (Moustafa et al., 2018), and in conditions including tumors (Erdogan and Webb, 2017; Despotovic et al., 2017) some of which undergo a SPARC-dependent ECM remodeling (Tanaka et al., 2019) which further point the implication of SPARC in ECM remodeling. Importantly, therapeutic targeting of ECM remodeling has also been described (Agarwal and Agrawal, 2017; van der Steen et al., 2017; Ito and Ohno, 2018; Islam et al., 2018). The ECM remodeling properties and its implications both in maintaining homeostasis and in pathological conditions (Ford and Rajagopalan, 2018) provide explanations on how adipocytes are modified in terms of expansion and tissue differentiation during a developing obesity which accrues when the energy balance is switched from a balanced status into a broken homeostasis (Ghanemi et al., 2018a). Thus, cellular and functional properties of remodeled adipocytes would require ECM remodeling that also depends on the adipocytes localization as well as on the ECM properties of each type of adipocytes (subcutaneous or visceral). Following the same line of thoughts, the SPARC deficiency would have an impact on the adipocyte ECM remodeling occurring during obesity and therefore, govern fat distribution. Such conclusion would be explained by the property of SPARC to bind and interact with different component of the ECM such as collagen type IV, vitronectin and fibrillar collagens (types I, II, III, and V) (Brekken and Sage, 2000) and thus affect adipocytes "rigidity" and expansion ability when compared to the adipocytes under balanced homeostasis.

Therefore, when fed with a HF diet, SPARC-deficient mice would store the extra energy in the subcutaneous AT rather than in the visceral AT. Such adiposity distribution pattern is towards a better metabolic profile because cardiometabolic benefits have been associated to subcutaneous AT (Tran et al., 2008a; Chen et al., 2018; Hocking et al., 2008; Tran et al., 2008b), whereas the visceral AT is associated with a variety of health problems including metabolic syndrome (Despres and Lemieux, 2006), cardiometabolic risk (Smith et al., 2012), coronary artery diseases and dysregulation of lipoprotein-lipid metabolism (Despres, 1992). However, this difference in fat storage between the subcutaneous AT and visceral AT is not seen in LF-fed mice. Indeed, although there is an increased adipocyte expansion in subcutaneous adipocytes compared to visceral adipocytes, the LF diet does not provide enough extra energy intake to create a positive energy balance (Fig. 1) (as in the HF diet) to reveal such differential ability to store fat between these two locations of AT. Therefore, no such difference is seen in LF-fed mice. This explains the contrast of the results reported above and point that links between SPARC and the fat distribution (visceral vs subcutaneous) which is in fact more important than the body weight in terms of health prognosis (Ghanemi et al., 2018a; Park and Lee, 2005; Neeland et al., 2019). The previous critical analysis of the works linking SPARC to adiposity allows us to hypothesize that SPARC-deficient mice will not become obese nor develop increased adiposity compared to WT mice when fed with a LF diet (Fig. 1). This is supported by a recent study showing that whereas both SPARC-deficient and WT mice fed with regular laboratory chow have similar body weights, SPARC-deficient mice fed with high-calorie diet (HF chow and sucrose added to drinking water) had an increased body weight compared to WT mice fed with the same high-calorie diet (Atorrasagasti et al., 2019).

Moreover, stage of adipogenesis is also affected by the type of expressed collagen which would also be affected by SPARC. Indeed, preadipocytes synthesize primarily collagen I (fibrillar) but differentiated adipocytes express primarily collagen IV (the prevalent collagen in basement membranes) as part of the ECM network (Smas and Sul, 1995) with the increased secretion of type IV collagen in association with adipocytes differentiation (Aratani and Kitagawa, 1988). This is of interest knowing that the association between collagen IV and adipocytes differentiation might also be behind the difference in adipogenesis between visceral and subcutaneous adiposity based on the dynamics of ECM (Mariman and Wang, 2010) leading to a fat distribution toward a developed subcutaneous adiposity (rather than a visceral AT) and eventually results in an improved insulin sensitivity and a lower metabolic risk (compared to a developed visceral adiposity rather than subcutaneous adiposity) (Despres et al., 1990; Després, 2012). In addition, SPARC-deficient mice had no significant difference in the circulating amount of insulin compared to WT (Bradshaw et al., 2003a). This would further indicate a higher insulin sensitivity because these SPARC-deficient mice had increased adiposity (Bradshaw et al., 2003a) for which insulin action is required due to the implication of

insulin in AT development (Dimitriadis et al., 2011; Emanuel Anna et al., 2017). However, the fact that SPARC-deficient mice have a developed subcutaneous AT, does not necessary mean less visceral AT but could indicate an increased ability to store the extra energy in the dermal AT. These SPARC-deficiency-induced modifications in the fat distribution could contribute to reduce central obesity and thus, resulting in a better metabolic profile with reduced risk for the metabolic syndrome and insulin resistance (Fig. 1).

Yet, the expressions of SPARC and the associated proteins (herein, collagens) pattern would be different depending on tissues, mouse strain and also age (Mansergh et al., 2007). For instance, whereas in the study of Norose et al. only 1.5 months were enough to observe the first posterior cortical opacities (cataract) in C57BL/6 J × 129 Sv F2 (exon 4 was targeted) mice (Norose et al., 1998), in the study that used MF1 × 129 Sv F2 background mouse strain (exon 6 was targeted for disruption) cataract was observed at around 6 months of age (Gilmour et al., 1998). These illustrates the effect of mouse strain on the effects of SPARC deficiency seen at different ages. This indicates that the degree of implication of SPARC in ECM remodeling (effect of SPARC deficiency) is different depending on the age (development stage) and thus can explain those "contradictory" results seen among the different SPARC deficiency studies (Norose et al., 1998; Gilmour et al., 1998). Studies in other species and different tissues have also been carried out and showed the different effects of either SPARC deficiency or SPARC overexpression that can be seen. As an illustration, the overexpression of SPARC decreased type IV collagen levels in the basement membrane ECM of anchor cells in *Caenorhabditis elegans* (Morrissey et al., 2016) and SPARC-deficient mesangial cells have a reduced expression of collagen type I (Francki et al., 1999). Such data further support the involvement of SPARC in cellular remodeling.

SPARC is known to inhibit adipogenesis, a pathway shown to involve beta-catenin signaling enhancement (Nie and Sage, 2009a,b). Following a HF diet, SPARC has been shown to be upregulated (epididymal adipose) in three different models of obesity (Tartare-Deckert et al., 2001). This SPARC upregulation could represent a homeostatic response to the HF diet in order to limit adipogenesis as regulatory feedback (Fig. 3) and maintain the energy balance. The possible induction of AT fibrosis resulting from the hyperleptinemia-induced upregulation of SPARC (Petersson et al., 2013) would also participate in limiting adiposity development. However the existence of factors that are also involved in adipogenesis such as collagens and that are also affected by SPARC expression (Francki et al., 1999; Bradshaw et al., 2002) could make that although SPARC inhibits adipogenesis, SPARC deficiency might not stimulate adipogenesis and could just remove the SPARC-induced adipogenesis inhibition (Nakamura et al., 2012). Within this context, Delany et al. (Delany et al., 2003) indicated that the absence of SPARC might influence adipocytes differentiations. However, the adipocytes described in this paper are bone marrow AT (BMAT) that have different properties from the adipocytes we focus on in obesity research which are white AT (both subcutaneous and visceral) in addition to the brown adipose tissue (BAT) as described by Hardouin et al. (Hardouin et al., 2016). In addition, the loss of bone due to the SPARC deficiency would affect the BMAT properties, which means that the modifications seen in the adipocytes of SPARC-deficient bone marrow would be the consequence of the reduced ability of osteoblasts for formation, maturation and survival that resulted from the SPARC deficiency. Adipocytes could even be a "replacement tissue" due to the fibrosis tissue limited ability to develop because it requires SPARC as a fibrosis promoter (Kos et al., 2009) which is absent in those SPARC-deficient mice. Importantly, (Hardouin et al., 2016) conclude that their finding does fit with the idea that SPARC governs and anti-adipogenic signal.

SPARC is involved in cell differentiation and development (Bradshaw and Sage, 2001). Since obesity is considered as a status of a "development" and turnover that seems to require SPARC, difference in SPARC expression between obese and non-obese models requires attention. In addition, SPARC expression should be interpreted differentially depending on whether it is expressed during an ongoing tissue development (such as adiposity growth during obesity (Tartare-Deckert et al., 2001)) conditions or rather is a non-developing tissue. Such way of thinking could emphasize that the overexpression of SPARC in obesity could be an adaptive feedback attempting to limit the adiposity expansion. This both correlates with results associating SPARC expression and AT hyperplasia in obese transgenic mice (Chavey et al., 2006) and the inhibitory properties of SPARC toward adipogenesis (Nie and Sage, 2009a,b). In addition, since ageing is a factor of body fat gain (St-Onge and Gallagher, 2010), SPARC deficiency effect on adiposity would be more noticeable in old subjects. In addition, since SPARC is important in muscle functions (as detailed in the next section), especially during exercise, the SPARC-deficiency could reduce muscular activity-related energy expenditure and therefore, with HF diet, would further enhance the positive energy balance and therefore, increase the energy storage which explains the increase of the HF diet-induced weight gain and AT depots in SPARC-deficient mice. Because of the impact of SPARC on the adipocytes ECM remodeling, the SPARC deficiency would increase the expansion ability of adipocytes. This ability is different between subcutaneous and visceral adiposity, and the distribution pattern would be towards an increased accumulation of the extra energy in the subcutaneous AT, thus leading to an improved metabolic profile and a healthier outcome compared to an adiposity accumulation within the visceral or ectopic locations.

3. The gene encoding SPARC as an "exercise-induced gene": a metabolic enhancer of the skeletal muscle

SM represents a key tissue of energy consumption since it accounts for an important ratio (50%) of energy expenditure of the body and around 40% of the body mass (Frontera and Ochala, 2015). Moreover, SM is responsible for around 70%–80% of insulin-stimulated postprandial glucose uptake (DeFronzo et al., 1981; Nuutila et al., 1994). Changes observed in the SM following exercise in term of cell differentiation, proliferation, mitochondrial functions and ECM remodeling are important to study at the molecular level in different ages. It allows to both elucidate the underlying mechanisms of important physiological and pathological pathways and the identification of potential therapeutic targets especially if we consider changes of muscle mass and metabolic functions associated with aging and the link with obesity (Biolo et al., 2014). Indeed, aging leads to muscle loss and dysfunction which affects the energy metabolism, including resting metabolic rate (St-Onge and Gallagher, 2010). Thus, aging represents an influencing factor in obesity development via increasing fat tissue especially for sedentary individuals (Biolo et al., 2014). Therefore, genetic factors affecting muscular metabolic performance would be easier to observe and evaluate in young subject since this metabolic performance (energy usage, contractility, etc.) decreases physiologically with age. Following this line of thought, effects of SPARC deficiency would be more significant in young subjects especially that SPARC expression in SM decreases with age as well (Scime et al., 2010; Nakamura et al., 2013).

Numerous research teams have shown that exercise enhances the expression of mitochondrial genes such as oxidative phosphorylation (OXPHOS) and improves physical fitness, lipid profile and insulin sensitivity (Riedl et al., 2010; JM, 1994). A cellular model of exercise (electrical pulse stimulation applied in myotubes culture) also showed that gene encoding SPARC is an electrical pulse stimulation-induced gene (Melouane et al., 2019). Its activity in linking mitochondrial properties and ECM would involve interaction with integrin-linked kinase/adenosine monophosphate-activated protein kinase (AMPK) pathway (Melouane et al., 2019). A study reported genes modulated in SM by mild exercise which can easily and safely be performed by elderly individuals (Riedl et al., 2010). This study has highlighted the importance of mitochondrial OXPHOS and ECM remodeling in the SM adaptation. Importantly, these results showed that the training at

lactate threshold (LT) induced 3 transcripts related to ECM, namely collagen type III alpha 1 (COL3A1), collagen type IV alpha 1 (COL4A1) and gene encoding SPARC, which accounted for 25% (3/12) of modulated transcripts in elderly (Riedl et al., 2010). However, in young adults, only 2 transcripts in the same function including collagen type I alpha 2 (COL1A2) were modulated, which corresponds to approximately 0.5% (Nishida et al., 2010). Although the only other study examining the effects of exercise on SM transcriptome in elderly subjects has used high-intensity (80% maximal heart rate) exercise, the exercise has also induced ECM-related genes such as genes encoding SPARC and COL3A1 (Radom-Aizik et al., 2005). The ECM associated protein, SPARC, specifically binds several ECM molecules including collagen types I, III and IV (Sage et al., 1989), thus influence both fibrous and basal lamina organization through growth factors binding, such as insulin-like growth factor (IGF), to mediate cell-matrix interactions (Francki et al., 2003; Mason et al., 1986b).

A Recent study has confirmed the induction of SPARC mRNA and protein expressions after exercise in SM of human and mice (Aoi et al., 2013). More importantly, increases in C2C12 myoblasts differentiation and expression levels of myogenin, COL1A1 and OXPHOS proteins after adding a recombinant SPARC protein have been described (Melouane et al., 2018). In addition, an improved collagen maturation was also reported following the overexpression of SPARC in WT mice (Schellings et al., 2009). These elements strongly suggest that SPARC represents an important factor in exercise-induced metabolic benefits and improvement of muscle structure and energy homeostasis profile; especially that exercise has been linked to ECM remodeling (Duarte et al., 2017) and an upregulation of SPARC has been reported during SM regeneration as well (Petersson et al., 2013). In contrast, lack of SPARC has been linked to modified expression of actin isoforms, led to post-fatigue recover inability (Jorgensen et al., 2017) and myofiber atrophy (Nakamura et al., 2013). This further support the concepts defining SPARC as specifically expressed according to a ‘temporal” pattern (Petersson et al., 2013) during tissue modifications including remodeling and repair (Jorgensen et al., 2009) rather than regeneration (SPARC deficiency does not affect SM regeneration (Jorgensen et al., 2017)) although there is an upregulation of SPARC during SM regeneration (Petersson et al., 2013). This could indicate that SPARC would be involved in complementary remodeling and repair functions during regeneration. In addition, the inhibitory properties of SPARC towards myoblast differentiation (Petersson et al., 2013) could be seen as a regulatory effect to control the SM hyperplasia and rather enhance SM metabolic performance instead of increasing SM cells number.

All together, these data allow us to map the links between SPARC expression and SM modification including during exercise and development (metabolic and functional) mediated by ECM and mitochondria as well as cytoskeletal (Fig. 2) because SPARC interacts, at least in part, with SM actin (Jorgensen et al., 2017). Since exercise induces the release of SPARC from the SM, considered therefore as a myokine (So et al., 2014), it would act, among other tissues, on the SM itself and therefore would be an “autocrine” factor.

Moreover, there is a decrease in both collagen type I (increase in AT) and physical activity in SPARC-deficient mice (Norose et al., 1998; Delany et al., 2000). In addition, 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR)-stimulated AMPK phosphorylation is reduced by small interfering RNA (siRNA) of gene encoding SPARC (Song et al., 2010). This is of interest because AMPK phosphorylation induces mitochondrial biogenesis via the activation/induction of the key regulator of mitochondrial biogenesis peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PPARGC1A, also known as PGC1α) (Lira et al., 2010; Jager et al., 2007; Wu et al., 1999) and thus, siRNA of gene encoding SPARC would reduce the mitochondrial biogenesis. This indicates that the deficiency or the down expression of gene encoding SPARC negatively affect the mitochondrial biogenesis and thus the OXPHOS capacity of the SM (cellular bioenergetics). In addition, the increase of adiposity without an increase in the body weight in SPARC-deficient mice (compared to WT) (Bradshaw et al., 2003a) could indicate a loss of lean mass (SM) as well. This would suggest an implication of SPARC not only in the ECM or mitochondrial functions but also in the SM building (myocytoskeletal). Whereas exercise is known to increase protein synthesis in aged SM (Reynolds et al., 2004), myoblasts from endurance-trained men exhibit higher glucose uptake (Berggren et al., 2005), probably via the induction of glucose transporter type 4 (GLUT4) expression by the training (Neufer and Dohm, 1993). Insulin plays important roles in the SM such as protein synthesis and glucose transport, and exercise improves insulin actions, which runs counter to aging (Riedl et al., 2010; JM, 1994; Harris, 2005; Drela et al., 2004). SPARC is known to modulate the interaction of cells with growth factors as well as to interact with AMPK and regulate GLUT4 expression (Francki et al., 2003; Song et al., 2010), which establishes more links between SPARC and muscular energy metabolism.

Based on the links among SPARC, its expression induction by exercise and exercise effects on SM, it seems logic to point SPARC as main factor in the SM remodeling and the exercise-induced SM metabolic changes. The implications of SPARC in heart, which is increased by β-adrenergic stimulation (Masson et al., 1998), seem to be comparable to those in SM. Indeed, following an induced myocardial infarction, prevention of cardiac dysfunction with an amelioration in collagen maturation in gene encoding SPARC-overexpressed mice, whereas the SPARC deficiency leads to an immature collagenous ECM and increased cardiac dysfunction (Schellings et al., 2009).

Unlike in the AT, the increased expression of SPARC (rather than its deficiency) is positive for the SM metabolic performance. Indeed, taken together, the previous reported observations show that SPARC is both induced by exercise and also required to mediate some of the exercise-induced benefits both in terms of tissue remodeling (adaptation) and metabolic functions enhancement (enhanced OXPHOS and glucose usages). Therefore, enhance the metabolic ability of the SM. With such SM enhancement properties, SPARC could be used therapeutically for diseases such as sarcopenia as well as disorders involving energy balances deregulation such as obesity. However, herein the missing link seems to be the elucidation of how SPARC affects the SM contractile properties, its mechanic and the SM cytoskeletal properties. Completing such aspect, would give a full image of how SPARC impact the SM both at the metabolic and structural (mechanic properties) levels.

4. Applications and therapeutic perspective

The data we have exposed show that SPARC is a multi-functional glycoprotein that has impacts on metabolism which support the theories linking the ECM to the mitochondrial function and metabolic modifications (Melouane et al., 2018). Furthermore, ECM remodeling has been reported following exercise training in visceral AT (Duarte et al., 2017) as well as with both obesity and exercise in SM as well (Martinez-Huenchullan et al., 2017). This reflects the complex interactions between ECM (impacted by SPARC modifications) and these two key metabolic tissues, AT and SM, that govern most of the energy flow (storage and expenditure, respectively).

Whereas the beneficial effects on AT are seen following SPARC deficiency, the improvement of muscular metabolisms seems to rather be the result of an overexpression of gene encoding SPARC (Fig. 2). Indeed, the SPARC deficiency would increase the adipocytes extension ability (and fat storage) of the subcutaneous AT more than in the visceral AT which would reduce the negative impacts of visceral adiposity and increase the benefits of a developed subcutaneous AT. However, in the SM it is rather the overexpression of SPARC that would lead to an improved metabolic profile with a better adaptation to exercise, whereas SPARC deficiency would have negative effects on SM such as a disturbed actin cytoskeleton. This indicates that although SPARC expression-induced ECM remodeling follow a similar pattern in muscles and adipocytes (especially in terms of collagen expression/

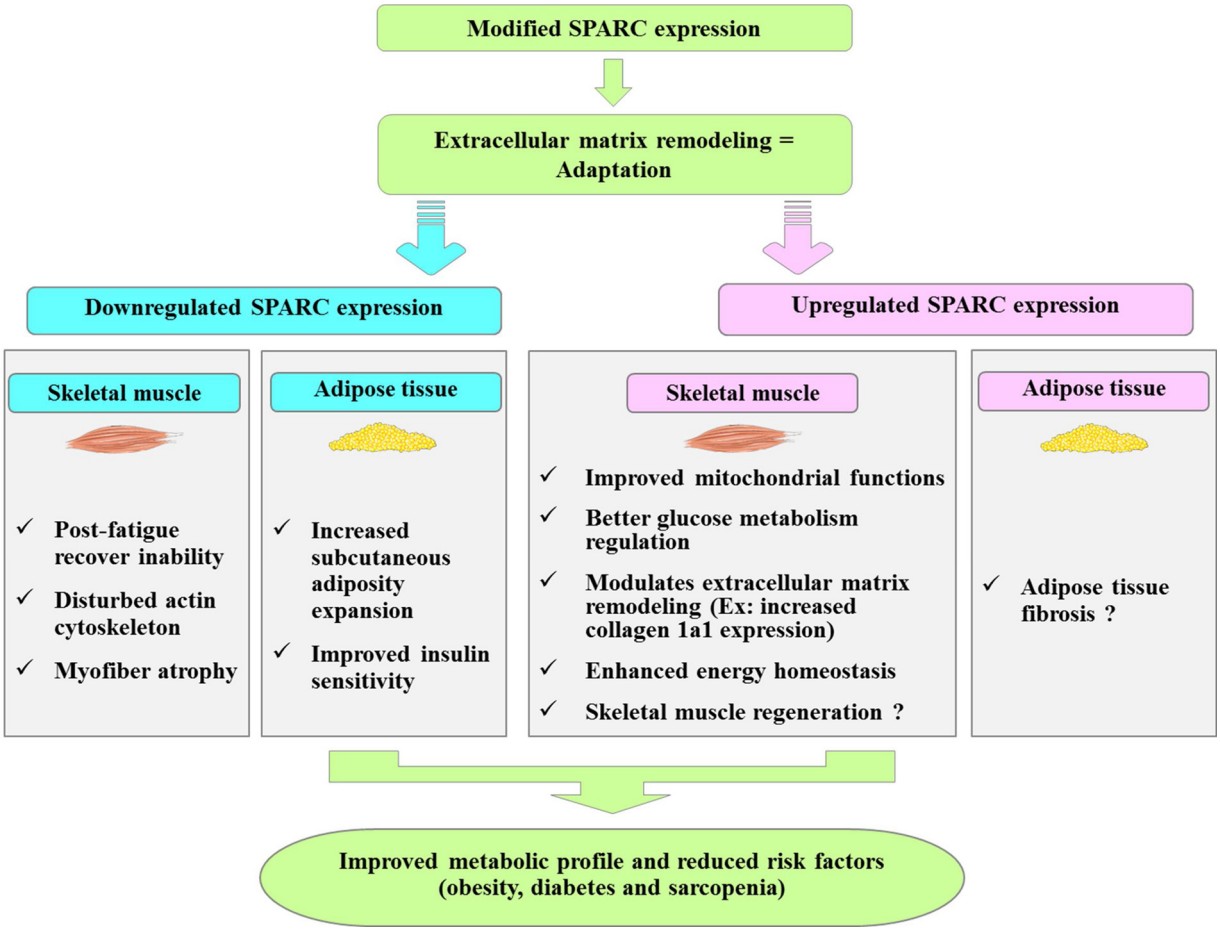

Fig. 2. SPARC seems to play different roles in these two tissues. Whereas, it ameliorates metabolic and structural properties of the skeletal muscles, SPARC-deficiency in adipocytes seems metabolically beneficial.
Abbreviation: **SPARC**: Secreted protein acidic and rich in cysteine.

maturation), it leads to different metabolic outcomes in these two tissues. Indeed, the consequences of SPARC deficiency are similar in both AT and SM (limit the development). However, SPARC deficiency leads to divergent phenotype in AT and SM because the functions of these two tissues are different. A developed muscle does increase energy expenditure whereas a developed AT does enhance the energy storage.

SPARC is produced by adipocytes into the circulation with concentrations that are in correlation with the body mass index (BMI) (Kos et al., 2009; Takahashi et al., 2001). In addition, the correlation between AT-derived SPARC with both fat mass and waist circumference (Kos et al., 2009) was also reported. This could also be put in the context of a correcting/balancing metabolic homeostasis via which adipose cells of obese individuals produce SPARC that will migrate ("hormone") to the SM in order to produce its effect of enhancing the metabolism and remodeling of the SM, which would improve muscle-dependent energy expenditure and thus, counter the increased caloric intake (beyond the elevated BMI) as an attempt to reestablish the energy balance. Additionally, the SM development is required to carry the excess body weight of obese subjects. This would also explain the AT production of SPARC that will increase SM functions. Following the same line of thoughts, and within the context of "re-establishing" the energy balance, the elevated concentration of SPARC in obese patients would be an attempt to limit the adipogenesis (via the adipogenesis inhibition properties of SPARC (Nie and Sage, 2009a,b)) and would follow similar pattern as leptin which is elevated in obese patients but fails to perform its action as an anti-obesity factor (leptin resistance) (Sainz et al., 2015) (Fig. 3). Indeed, the increased serum concentration of leptin can also be seen as an attempt to establish the energy balance via the properties leptin to limit food intake and increase energy expenditure (Halaas et al., 1995). However, since leptin fails to balance the energy homeostasis (leptin resistance (Myers et al., 2012)) in obese patient, the raising question would be whether or not we have a "SPARC resistance" in obesity leading to the loss of the adipogenesis inhibition properties of SPARC. This theory is further supported by the ability of both leptin and insulin (also elevated during obesity (Wang and Liao, 2012)) to enhance SPARC production in AT (Kos et al., 2009), whereas glucose decreased it (Kos et al., 2009). Thus, these observations put SPARC within the pathways involving leptin, insulin (Fig. 3) and glucose in energy homeostasis regulation especially that SPARC is required for both insulin secretion and glucose homeostasis (Atorrasagasti et al., 2019).

This could support the concept defining the role of a factor (hormone, transmitter, etc.) depending on the status. SPARC would not have the same properties in healthy status (balanced energy homeostasis) as it has during broken homeostasis (obesity, diabetes, sarcopenia, etc.).

In addition, the known implications of mitochondria in ageing, especially within AT and SM (Boengler et al., 2017), would justify the need to investigate SPARC roles during the ageing process and its eventual interactions with reactive oxygen species (oxidative stress) (Aseer et al., 2017) that play roles in diabetes (Panigrahy et al., 2017), ageing (Korenevsky et al., 2017), inflammation (Hsu et al., 2018), obesity (McMurray et al., 2016) and sarcopenia (Jackson, 2016; Vasilaki et al., 2017). Indeed, ageing (with the free radicals accumulation, decreased biological function, etc.) represents a risk factor for many diseases including metabolic disorders.

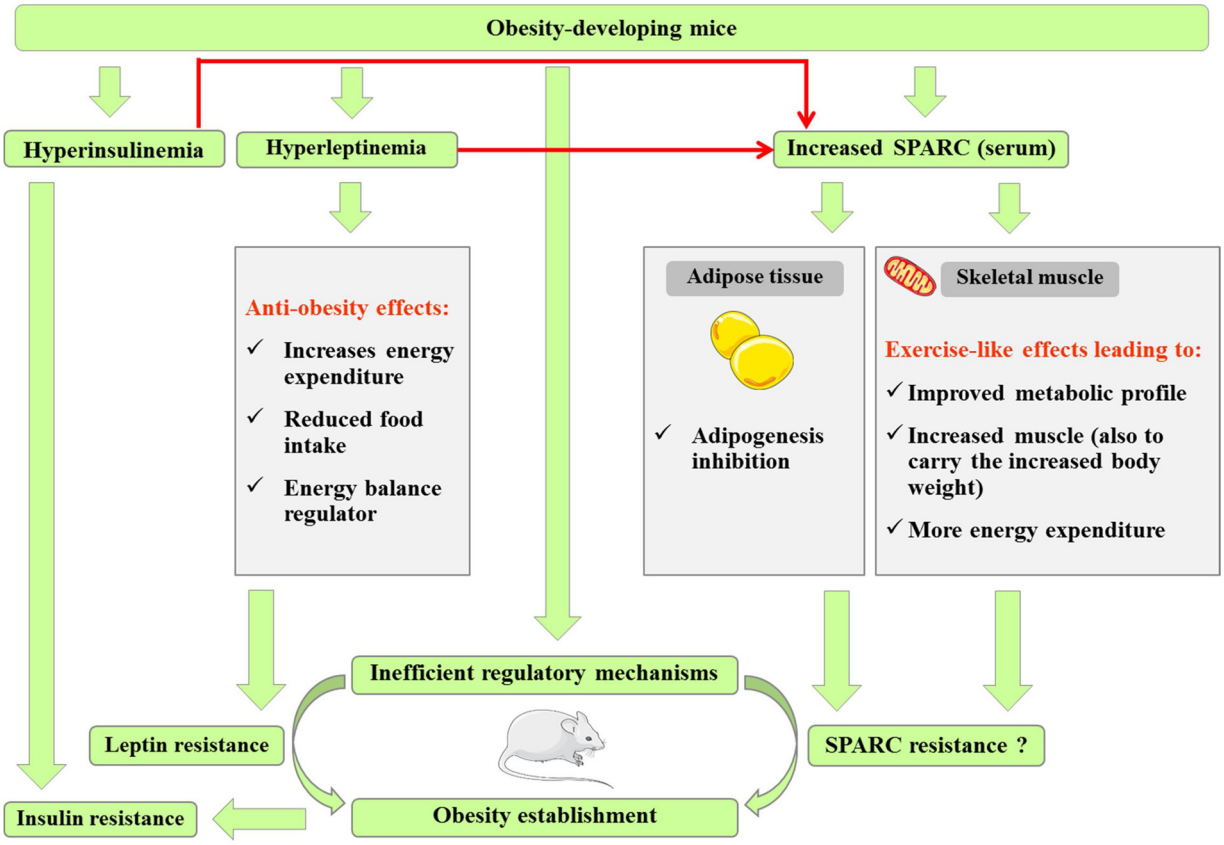

Fig. 3. SPARC as an obesity-induced factor: An attempt to re-establish energy balance.
Abbreviation **SPARC**: Secreted protein acidic and rich in cysteine.

Studying the functional and, more importantly, the metabolic implications of SPARC in other tissues and organs, especially other key metabolic tissues such as the liver and the brown AT will be the next step to map the metabolic profile of SPARC within the homeostatic balance. The hormonal changes (leptin, insulin, etc.) are also another key step within this path, since leptin and insulin induce SPARC expression in adipocyte (Kos et al., 2009). Importantly, mapping these pathways should take into consideration the different related influencing factors such as the healthy status (obese or lean), the activity level (sedentary or active) and the type of diet (HF, LF, high sucrose, etc.). The effects of SPARC on cells does not only depend on tissues (AT and SM in our examples) but also on the status (and its stage, whether advanced or early), the factors and the environment to which the tissue is exposed (normal, cancer, obesity, development, exercise, etc.).

Therapeutic targeting (gene therapy, pharmacological agents, etc.) of SPARC or gene encoding SPARC-related pathways in obesity for example would require a precise therapy (such as new generations of therapeutic vectors) and an increased pharmacovigilance. Precisely, the targeting would require to increase SPARC expression (or enhance the pathways it activates) in the SM and/or inhibit (or reduce) the expression of these glycoprotein in the AT (preferably the subcutaneous AT so that the adiposity accumulation would be towards the subcutaneous AT rather than the visceral AT). Such approach could provide efficient therapies for obesity, diabetes, sarcopenia and sarcopenic obesity especially that increasing publications describe targeting ECM (Agarwal and Agrawal, 2017; van der Steen et al., 2017; Ito and Ohno, 2018; Islam et al., 2018). Importantly, the described effects of SPARC-modified expressions in both AT and SM leads to discuss the sarcopenic obesity for which age is the main factor and which involves these two tissues and combine the loss of muscle mass with an increase in fat accumulation (Polyzos and Margioris, 2018). Therefore, put a spotlight on SPARC-based therapy (combined with sufficient protein intake) as a good choice to both improve muscle performance and reduce adiposity especially for individuals who are unable to perform the required exercise. In this last case, we would obtain an “exercise pill” that would pharmacologically mimic the exercise benefits at the SM via stimulating the SPARC induced effects.

None (The authors declare that there is no conflict of interests).

Declaration of Competing Interest

None (The authors declare that there is no conflict of interests).

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