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Review Article

CURRENT KNOWLEDGE ON OVINE GLUCOSE 6-PHOSPHATE DEHYDROGENASE (G6PD): FROM ENZYMATIC ACTIVITY TO -OMICS APPROACHES AND FUTURE PERSPECTIVES

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A B S T R A C T

Glucose 6-phosphate dehydrogenase (G6PD), a cytosolic enzyme encoded by a housekeeping X-linked gene, catalyzes the first committed reaction of the pentose phosphate shunt. The enzyme became known due to its involvement in hemolytic cases, known as G6PD deficiency in human. Its main function is the production of NADPH which is further used, also, oxidative substances and in reductive biosynthetic reactions. In sheep, it plays also a crucial role in the de novo synthesis of fatty acids, rendering it as a potential marker of lipogenesis. The present review highlights all the advances conducted so far regarding the ovine G6PD from the early stage of enzymatic level up to the novel approaches of molecular and proteomic level. Where necessary, human counterpart is used as a reference to point out the importance of the findings. The -omics approaches are discussed as a tool for future potential control of fatty acid synthesis and ovine products' quality improvement. Future perspectives are also discussed. The here presented information may form a basis for scientists to develop new approaches in the field of ruminant's lipogenesis.

INTRODUCTION

Animal products with low-fat content as well as high and consistent quality are more preferable by consumers the last decades. This led animal production to invest on research related to the area of fatty acid synthesis (lipogenesis), as a vehicle to improve products' quality (i.e. meat, milk). Lipogenesis is considered of utmost importance in a ruminant's livestock. Excess fat deposits influence negatively the grading of carcasses (Hood and Thornton, 1979; Belk *et al*., 1993). Contrary, in some cases, high intramuscular fat deposition (marbling) is considered a desired characteristic of meat quality (Vernon, 1981). Besides, the dynamics of adipose tissue metabolism, especially during puberty or pregnancy, is related to health status (i.e. ketosis or toxemia) as well to future reproductive and milking performance (Rogdakis *et al*., 1997).

Sheep livestock forms a vital economic axe in affluent as well as in less affluent countris. It offers great amounts of meat and milk, which either consumed directly or transformed with further processing into other types of livestock products (i.e. cheese, yoghurt, meat products). Despite the significance of the sector, ovine products and especially lamb meat have been accused for high fat and cholesterol content, rendering consumers' preference on such products under high susceptibility.

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Thus, the elimination of fat content in ovine products, especially meat, could offer novel marketing alternatives and further boost on the sector.

Glucose 6-phospahte dehydrogenase (G6PD) is widely known as an enzyme due to its involvement in human hemolytic cases, known as G6PD deficient cases (for review see Beutler, 2008). It is the rate limited enzyme of the pentose phosphate shunt being important for the regeneration of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and the production of pentoses and ribose-5-phosphate for further nucleotide synthesis. Besides, in sheep G6PD is considered as one of the major lipogenic gene due to its major contribution to the synthesis of fatty acids by terms of the required reducing power (NADPH), rendering it as an option to control lipogenic activity. Herein, we present the recent advances on the ovine G6PD (oG6PD) discussing, also, further future perspectives by terms of lipogenic approach and productive traits.

Biochemical aspects

The pentose phosphate shunt (PPS) plays a crucial role in ruminant's lipogenesis as it contributes to the necessary reductive power (NADPH) in the *de novo* synthesis of fatty acids. Glucose 6-phosphate dehydrogenase (G6PDH) is considered the key and rate limiting enzyme of the aforementioned biochemical shunt (Figure 1). It catalyzes the first committed reaction of the shunt converting the glucose 6-phosphate to 6-*δ*-phosphoglucono_lactone, which is hydrolyzed spontaneously to 6-phosphogluconate (6PGD). G6PD comprise also the major source of the required amounts

of NADPH used for the reduction of acetyl-CoA to fatty acids. The contributed amounts of NADPH together with that produced by 6-phosphogluconate dehydrogenase (6PGD), range from 30-80% and sometimes up to 100% in ruminants. This depends on specie (cow or sheep), the productive stage and the external stimuli that animals may face (Vernon *et al*., 1981). Apart from PPS as a source of reducing power, NADPH produced by other sources may also contribute to the fatty acid synthesis. Cytosolic malic enzyme (ME) and isocitrate dehydrogenase (IDH) are, also, considered essential donors of reductive power not provided by the PPS. However, the predominant metabolic sequence of citrate to pyruvate is not significant in ruminants, rendering cytosolic ME a minor donor of NAPH unlike to non-ruminant species. With regard to the cytosolic IDH, it provides the rest of NADPH not produced by the pentose phosphate shunt (Vernon, 1981).

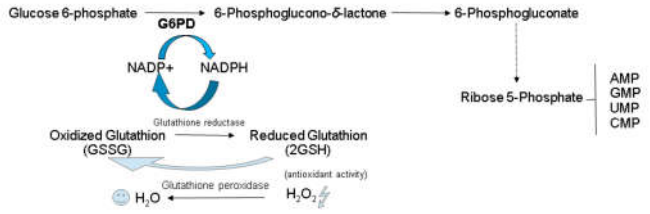

Figure 1 G6PD contribution to biochemical pathways.

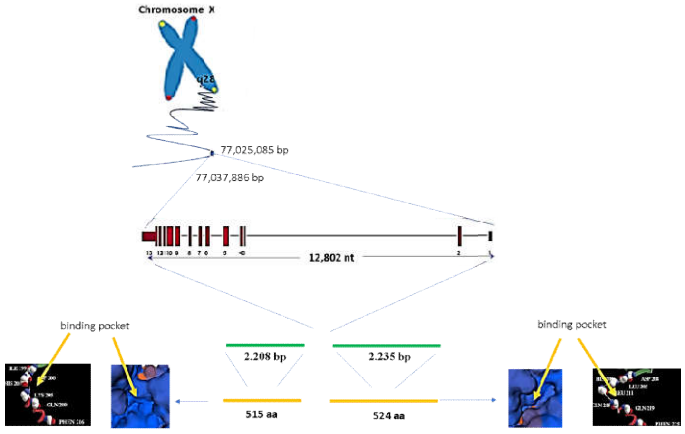

Figure 2 Genomic and protein structure of ovine G6PD.

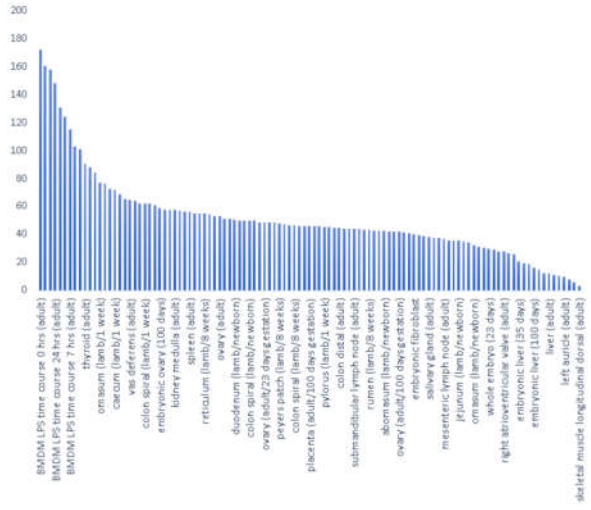

Figure 3 G6PD expression in various ovine tissues.

Apart from PPS, G6PD influences also indirectly the biochemical pathway of glutathione, protecting cells from oxidative damage. Specifically, it regulates the formation of the reduced form of glutathione from its oxidative form. The amounts of NADPH produced by the G6PD action through the PPS keep up the supply of reduced glutathione in the cells rendering the elimination of free radicals in cells more effetive (Figure 1).

Enzymatic activity of ovine G6PD

G6PD enzymatic activity has been well studied in many eutherian species, by terms that modulates cellular homeostasis by controlling redox index via the regeneration of NADPH. Especially in human beings, many fluctuations of its activity have been observed mainly due to genetic disorders, which lead to hemolytic cases either lethal or treatable. More than 400 million individuals are affected worldwide. In such deficient, cases, it is red blood cells, which carry oxygen to tissues that are mainly affected as the rhythm of cells destroy is faster than that of replacement leading to hemolytic anemia (review in: Buetler, 2008; Luzzato *et al* 2016; Belfield and Tichy, 2018; Luzzatto and Arese, 2018). In other species, like rodents, G6PD also plays a crucial role especially on oxidative damage. Nobrega-Pereira *et al*. (2016) reported that a modest increase of G6PD activity in transgenic mouse assists to improve health span and protected animals against oxidative damage. Hormones i.e. insulin or thyroid hormone induce also the levels of G6PD, while glucagon suppressed it (Kletzien *et al*., 1994). High carbohydrate or low-fat diet increase G6PD activity. Recently, Taniguchi *et al*. (2016) reported that rats fed with low protein diets showed induced levels of hepatic G6PD activity as a result of the low GSH levels and the amplified insulin response. Analyzing further the effect of different stimulus on G6PD enzymatic activity of these species is out of the purpose of this review.

Thus, focusing on ovine specie, as G6PD plays a crucial role in the synthesis of fatty acids, its levels (either enzymatic or transcriptional) may serve among other traits as a marker in further cross breeding schemes in regard to the desirable fat content of the final product. Similar approach has been described in pigs previously, where the levels of NADPH dehydrogenases used to develop a selection program on back fat (Rogdakis *et al*., 1996). The study of ovine G6PD activity has been the principal focus of the studies especially before the rapid development of the field of gene technology. Alterations of ovine G6PD activity has been well documented. A majority of studies revealed the fluctuation of enzyme's activity to a wide range of different stimulus such as diet composition, age, parasitemia, antibiotics, fluoride intoxication or energy intake (Piperova and Pearce, 1982; Travis *et al*., 1985; Beydemir *et al*., 2003; Yur *et al*., 2003; Laliotis *et al*., 2009; Esmaeilnejad *et al*., 2014). Piperova and Pearce (1982) reported a significantly greater G6PD enzymatic activity in adipose tissue extracts from sheep fed concentrate diets compared to that of grass-fed animals. Antibiotics like gentamicin sulfate and vancomycin hydrochloride inhibited the G6PD activity *in vitro* (Beydemir *et al*., 2003). Yur *et al*. (2003) reported significant lower levels of G6PD blood activity in fluorotic sheep compared to control animals. Low levels of ovine G6PD enzymatic activity have been reported in adipose tissue during low energy intake (Laliotis *et al*., 2009). A synchronized enzymatic activity of G6PD in respect to the activities of the

other three NADPH-producing enzymes (IDH, ME, 6PGD) in ovine adipose tissue has been also observed (Rogdakis *et al*., 1997; Laliotis *et al*., 2009). Esmaeilnejad *et al* (2014) reported decreased levels of blood G6PD activity in infected sheep by babesiosis compared to healthy animals. The aforementioned studies reveal the importance of ovine G6PD enzymatic activity fluctuations rendering its levels a valuable criterion either to assess the general lipogenic activity or the oxidative status of the studied animals.

Approaches at molecular level

At molecular level, the gene encoding G6PD has been well studied in human, mouse and rats (Persico *et al*., 1986; Chen *et al*., 1991; Zollo *et al*., 1993; Ho *et al*., 1988) as well as in other non-mammalian species i.e. Drosophila (Fouts *et al*., 1988 [23]) very early, mainly because the importance of the enzyme in human deficient cases and also due to the efforts of finding animal models for studying further treatments of human cases. Although ovine G6PD cDNA sequence and its promoter region have been cloned and characterized (Laliotis *et al*., 2007a,b) information about the genomic structure of the gene was missing until few years ago. The advent of high-input technology and the implementation of Next Generation Sequencing shed light into new approaches on molecular level. Sequential information about the whole ovine genome (*Ovis aries*) has been already released in the fourth annotated full version (Oar_v.4) as an effort of the International Sheep Genome Consortium (Archibald *et al*., 2010), rendering easier further analysis on genes of major interest. G6PD gene spans between the 77,025,085 bp and 77,037,886 bp of the ovine X chromosome (NCBI). It consists of 13 exons, with the first exon being non-coding. The gene is transcribed into a cDNA sequence of 2.208 bp (short transcript / OG6PDA) translated into a protein of 515 amino acids. Whether a splicing event occurs, cDNA length consists of 2.235 bp (long transcript /OG6PDB) resulting in a protein molecule of 524 amino acids (Figure 2). It shares, also, high similarity (>85%) with human, cow and goat counterparts both at nucleotide and protein sequence (Laliotis *et al*., 2007a). The gene found to be expressed in many analyzed tissues (Figure 3) from the early beginning of sheep embryo's life up to the adult life span (Laliotis *et al*., 2007a; Clark *et al*, 2017) minoring the vital importance of the gene. In addition, the long cDNA transcript (OG6PDB) revealed to be expressed only in tissues where lipogenesis is higher in ruminants (Laliotis *et al*., 2007a).

Focusing on translational level, an *in-silico* 3D approach revealed structural changes between the two protein molecules derived from the respective ovine cDNA transcripts (Figure 2). Specifically, the observed frameshift on the amino acid sequence at the longer protein molecule (524 a.a) lead to the formation of a bigger catalytic binding "pocket" of the molecule compared to the short length protein molecule (515 a.a.), promoting the hypothesis that the catalytic action of the certain molecule is conducted in a less efficient manner and in respect to different external stimuli (Laliotis *et al*., 2007a). In this line, a lower relative transcript abundance of OG6PDB cDNA transcript have been observed in tissues where both transcripts are expressed (Laliotis *et al*., 2007a), enhancing the aforementioned hypothesis. Besides, changes in energy intake in lactating ewes revealed to play a crucial role in the protein expression of both ovine G6PD isoforms in adipose tissue. Negative energy intakes did not favor ($P>0.05$) the predominance of any particular protein isoform by terms of expression levels, contrary to highly positive intakes, where the protein expression of the short isoform was significantly higher in respect to the longer isoform expression (Triantafyllopoulos *et al*., 2014).

Single nucleotide substitutions are considered as a valuable source of genetic variability (Uppu *et al*., 2018). Although a numerous nucleotide substitution is observed throughout a genome, only the non-synonymous SNPs (nsSNPs) are considered of crucial importance, because they lead to changes in the open reading frame of the translated amino acid sequence. Whether such substitutions are linked with a physiological or productive trait, they can serve as a potential selection marker among others for future implementation of breeding schemes. In regard to the ovine G6PD gene, a total of 305 variations (SNPs) have been reported, either in coding or non-coding regions of the gene (Laliotis *et al*., 2018). Among them, six nucleotide substitutions have been characterized as nsSNPs, three of which have been revealed computationally that cause a lethal effect into the amino acid change (R136C; P396L; P489S). These three substitutions have been also found to resemble sequentially with human haemoelytic anemia and G6PD deficient cases (Laliotis *et al*., 2018), suggesting that they may related with unnormal enzymatic response in ovine organism. A decrease G6PD enzymatic activity in ovine blood similar to that observed in human G6PD deficient cases has been reported previously (Maronpot, 1972; Moore *et al*., 1981; Edward *et al*., 1986). Although the observed lower enzymatic activity, sheep showed resistant to known reagents causing intravascular hemolytic response in humans (i.e. fava beans, primaquine), indicating that sheep as an organism are not occurred as G6PD deficient in the same sense as human with similar (deficient) G6PD levels (Maronpot, 1972). Besides, sheep may also have an adaptive mechanism which reduces the oxidative stress of erythrocytes during their response to toxic stimuli like ozone (Moore *et al*, 1981) However, until recently none linkage between low ovine G6PD enzymatic levels and nucleotide changes has been reported, contrary to human cases, where a great number of such substitutions have been observed resulting in the majority of the reports in disease (deficiency) or lethal situations (Beutler, 2008; Luzzato *et al*., 2016).

In regard to the ovine G6PD promoter region, the specific region has been cloned and characterized (Laliotis *et al*., 2007b). Apart from a CAAT box, all other typical motifs of a promoter region like TATA box, GC rich regions, SP1 and AP2 binding factors were noted. In addition, a lot of cis-regulatory elements like SREBP, E-boxes and USF motifs were detected, indicating the transcriptional response of the gene towards external stimuli of lipid metabolism (i.e. polyunsaturated fatty acid diet, high insulin intake etc). Although it shares many conserved blocks compared to other mammalian species, information is still missing about variations among not related animals of the same breed or even among different breeds. The observed synergic action of ovine G6PD dehydrogenase together with the rest three NADPH-producing enzymes (6PGD, IDH, ME) described by previous authors (Rogdakis *et al*., 1997) implies a possible involvement of a common "actor" at transcriptional level. Insulin or insulin-like motifs, could be hypothesized to act such a role, but further characterization of the promoter region of the respective genes encoding the three aforementioned NADPH-

producing enzymes should be firstly achieved, in order such hypothesis to be verified.

Conclusion and future perspectives

In conclusion, sequencial information of ovine G6PD gene has been achieved and further characterization of functional gene regions have already been reported, assisting further research to be conducted not only on genetic level but also on linking genetic differences to (any) observed differences at biochemical and/or physiological level. Investigation of the potential association of the observed lethal mutations of G6PD gene with any biochemical characteristic (i.e. low G6PD enzymatic activity) or productive traits i.e. milk fat content, carcass quality/marbling, would be a future challenge. Moreover, the further elucidation of biochemical role of the longer G6PD transcript in respect to different stimuli apart from energy intake would also promote knowledge regarding ovine lipogenesis. Another aspect that remains unexplored in the ovine G6PD gene is the response of its promoter region (promoter expression patterns) in regard to various stimuli. Screening for mutations on this region among different sheep breeds (i.e. among fat and thin tail breeds or meat and wool breeds) would also offer new insights on ovine fatty acid synthesis. The investigation of G6PD enzymatic levels among different ovine breeds may offer new concepts for reevaluating sheep as a model organism for human G6PD deficient cases.

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