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► To cite this version:

Patrice Martin, B Badaoui, Daniela Barile, Hichem Lahouassa, Christian Beauvallet, et al.. AlphaS1-casein deficiency recorded for defective genotypes induces a chronic ER stress and deep changes in milk composition, signing a singular secretion process in goats. European Regional Conference On Goats, Jun 2013, Tromsø, Norway. , 2013, Goat Milk Quality. hal-01193994

HAL Id: hal-01193994

<https://hal.science/hal-01193994v1>

Submitted on 3 Jun 2020

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AlphaS1-casein deficiency recorded for defective genotypes induces a chronic ER stress and deep changes in milk composition, signing a singular secretion process in goats

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The extensive polymorphism recorded at the CSN1S1 locus has been shown to influence goat milk composition and its technological properties. A deficit in alphaS1-casein is responsible for the accumulation of immature caseins in distended rough endoplasmic reticulum (ER) cisternae of mammary epithelial cells (MEC). This triggers a chronic ER stress which induces, in turn, an adaptive unfolded protein response (UPR). Our data strongly suggest: i) the existence of a membrane-associated form of alphaS1-casein, which is required for efficient export of the other caseins from the ER to the Golgi apparatus; ii) that alphaS1-casein plays a key role in the early steps of casein micelle biogenesis. A differential proteomic analysis (2D-DIGE) of milks from goats of extreme genotypes (A/A vs. O/O) at the CSN1S1 locus revealed the over representation of ER-resident proteins in O/O milks, strongly suggesting a singular secretion mechanism for this genotype. In addition, goats of O/O genotype produce fat globules smaller in size and displaying significant differences in MFGM composition, including both MFGM proteins and polar lipids. A relationship between genotypes at the CSN1S1 locus and the profile (structure and composition) of milk free oligosaccharides (OS), which are also built within the ER, has been shown, thus providing additional evidence for the impact of alphaS1-casein deficiency on the functioning of MEC.

Finally, using different functional genomics approaches, we succeeded in highlighting the general dysfunction occurring in MEC from alphaS1-casein deficient animals, and in identifying genes contributing to the adaptive UPR and proteins involved in the transport between the ER and the Golgi apparatus, as well as enzymes participating to the biosynthesis of lipid droplets, the precursors of MFGs. Taken together our results demonstrate that a close mechanistic relationship exists between biosynthesis and secretion pathways of the main milk components: casein micelles, milk fat globules and oligosaccharides. We definitely demonstrated the relevance of the goat model as an experimental system to unravel the underlying mechanisms and to appraise the possibility to dissociate these biosynthesis pathways in order to modulate selectively one or the other.

Acknowledgements

We thank the staff of the INRA experimental unit from Bourges, La Sapinière, without which this work could not be carried out. A large part of this work was funded by ANR (Genanimal program) and APIS-GENE.