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# 57. Milk metabolite profiles in goats selected for longevity support link between resource allocation and resilience

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## Abstract

The aim of this study was to assess the use of milk metabolites as an indicator of resilience. Hyper-selection based on functional longevity of AI bucks successfully created two groups of goats with different lifespan. Furthermore, the higher body weight of high longevity line goats and lower milk fat:protein ratio during the beginning of the first lactation suggested different resource allocation profiles between lines. Finally, the difference between the two lines of goats in milk metabolites evolutions during an imposed underfeeding challenge supported this hypothesis. These preliminary results support the value of milk metabolites as a promising noninvasive proxy related to resilience in dairy ruminants.

## Introduction

Resilience is the ability of a goat to cope with environmental disturbances, such as pathogens or feed restriction. Genetic selection on resilience remains a challenge. Because resilience translates into enhanced functional longevity, we created two lines of Alpine goats using hyper-selected bucks with the most extreme estimated breeding values for functional longevity. Recent literature showed evidence of a relationship between indicators of body fatness dynamics and resilience (Savietto *et al.*, 2015). In the present study, we explored the evolution of metabolic pathways related with lipomobilisation during feed restriction among goats selected for extreme functional longevity. Accordingly, an experiment was carried out in which time-series measurements of 14 milk metabolites were made in dairy goats exposed to an underfeeding challenge during early lactation. The aim of this study was to validate the use of milk metabolites as an indicator of resilience.

## Materials & methods

**Experiment.** Following the method developed by (Palhière *et al.*, 2018), we made a hyper-selection of dairy goats based on the genetic evaluation for functional longevity of 8,787 alpine AI bucks. From 2017 to 2021, two lines of goats were bred in an INRAE experimental farm (Bourges, France; Ethics approval C18-174-01) comprising 212 low longevity line (low\_LGV) and 228 high longevity line goats (high\_LGV). The following measures were regularly registered by trained technicians: serum immunoglobulin G concentration (IgG) at birth, monthly weight, health treatment, milk production, milk somatic cell scores (SCS), death/culling date.

In 2020, 49 primiparous dairy goats were exposed to a 2-d underfeeding challenge during early lactation (mean days in milk=39, SD=11). The challenge consisted of a 7-d control period (day -7 to 0) with a standard diet composed of forage and concentrate, 2 d of straw only feeding (day 1 and 2), and a 4-d recovery period on the standard diet (day 2 to 6). Prior to the start of each challenge period, the goats received the standard diet from parturition onwards. The goats were milked twice per day. From the beginning of

the prechallenge control period until the end of the postchallenge recovery period, concentrations of 14 milk metabolites were measured daily from the morning milking: glucose-6-Phosphate (Glu6P), glucose (Glu), galactose (Gal), beta-hydroxy-butyrate (BOHB), isocitrate (Isoc), glutamate (Glu), NH<sub>2</sub>, lactate dehydrogenase (LDH), Urea, Cholin, Malate, urate, triacylglycerol (TAG), cholesterol (Chol).

Animals were cared and handled in accordance with the French legislation on animal experimentation and European Convention for the Protection of Vertebrates Used for Experimental and Other Scientific Purposes (European Directive 86/609) under specific authorization number APAFIS#8613-2017012012585646.

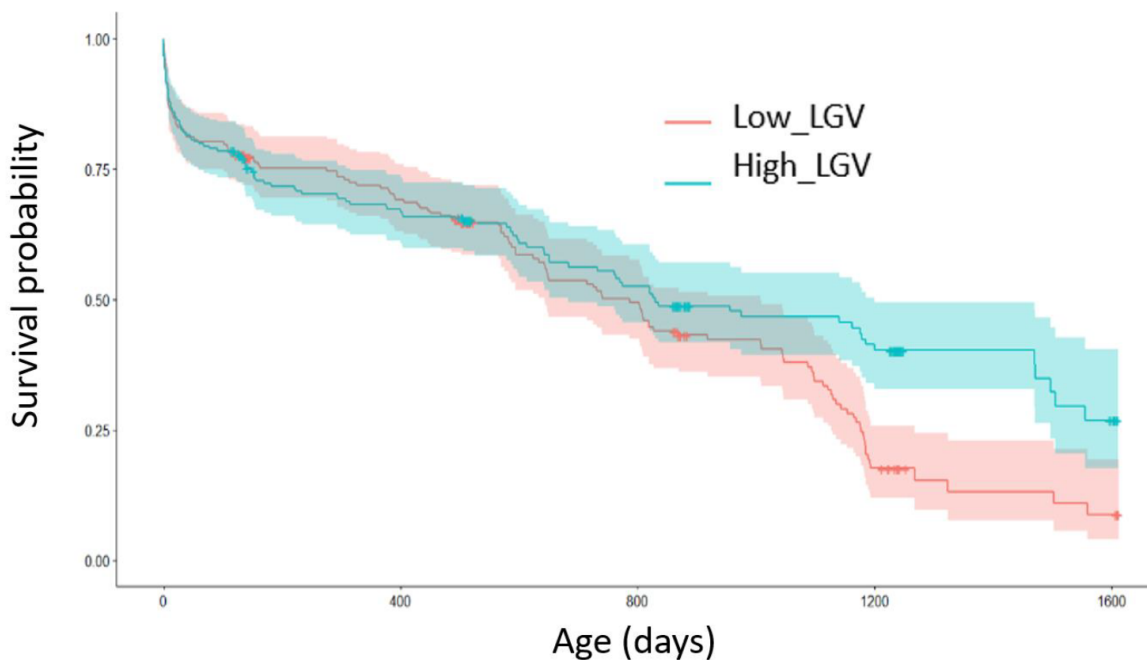
**Survival analysis and linear models.** The R package ‘survival’ was used to compare lifespan between the two lines. Survival analysis was performed using a Cox model. The model included both fixed covariate (line, year of birth, IgG at birth), and time-dependent covariates: weight, health treatment events (Zhang *et al.* 2018). Moreover, we ran linear regressions using the lm and glm procedures in R in order to compare between the two lines: weight at birth, monthly weight, IgG at birth, first lactation milk yield at DIM 90 and 250 (MY90, MY250), milk fat: protein ratio and SCS.

**Functional principal component analysis.** We characterized milk metabolite profiles upon challenge using a functional PCA (fPCA) for each milk metabolite (Yao *et al.*, 2005). The daily concentration of each metabolite during the whole challenge period was included in the fPCA. We used the R package ‘fdapace’. This performs local linear smoothing on the covariance matrix and then estimates the principal components with conditional expectation method. Each individual milk metabolite curve was then characterized by a PCscore for each component. We chose the number of components as the minimum needed to explain 80% of the variance of the dataset.

**Sparse PLS DA.** We then used Sparse PLS-Discriminant Analysis (sPLS-DA) to evaluate the ability of milk metabolites to distinguish the longevity lines. This is a linear multivariate model which performs classification tasks and is able to predict the class of new samples (Lê Cao *et al.*, 2011). The method integrated a continuous data matrix comprising the individual PCscores and a categorical outcome variable: the line of the goat (high/low\_LGV). sPLS-DA seeks the components that best separate the sample groups, and also selects variables that best discriminate between groups using lasso penalization. We chose the number of components using cross validation on a non-sparse model (comprising all variables) and then tuned the number of variables to select on each component. We assessed the final performance of the model using a 5-fold cross validation.

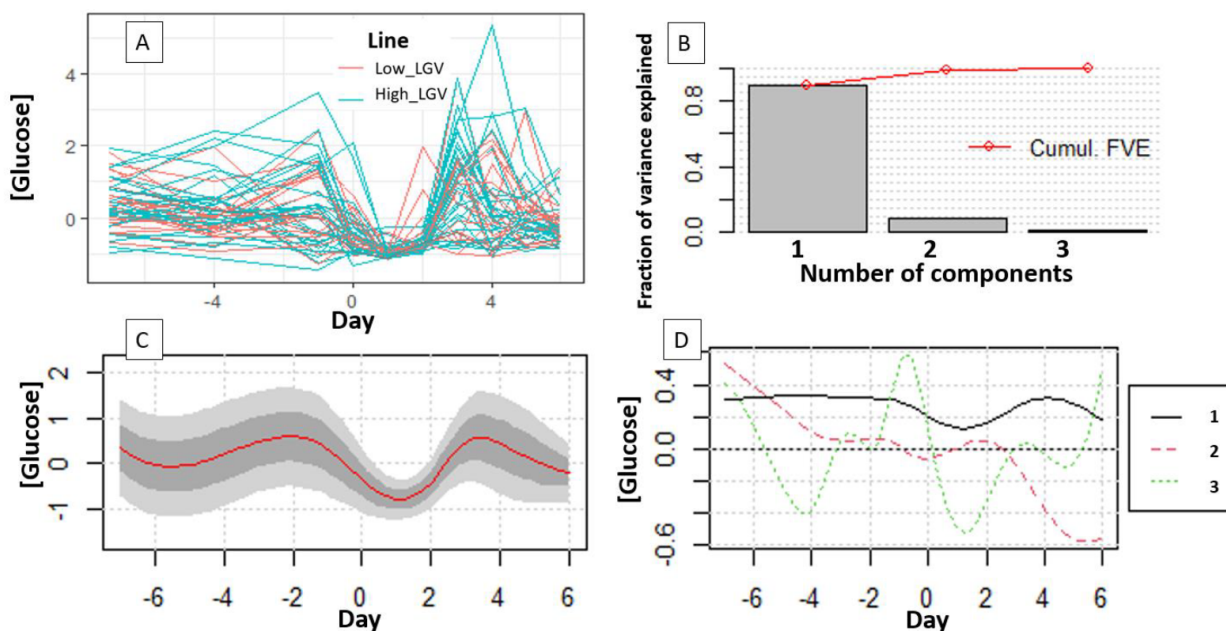
## Results & discussion

**Comparison of the two longevity goat lines.** Weight and growth during the first year of life were similar in both goat lines. In contrast, the low\_LGV goats had a lower weight during the beginning of first lactation than high\_LGV goats. The milk fat to protein ratio was also significantly higher in low\_LGV goats during first lactation. The overall survival (from birth to death) of high\_LGV goats was significantly greater than low\_LGV goats (hazard ratio=0.63, CI=0.47;0.86) even after we included treatment, growth, IgG at birth, and year effects, in the model (Figure 1). The line effect was not constant over time: no significant effect was found during the first year of life and the difference emerged after first kidding. This suggests that survival at an early stage of life and during later productive life are under different genetic regulation. These results support the hypothesis that the two lines of goats present different resilience levels and that this may be linked to different resource allocation profiles between lines. The analysis of milk metabolites profiles should contribute to validate this hypothesis.



**Figure 1.** Plot of Kaplan–Meier curve showing survival against time for high longevity line (high\_LGV) and low longevity line (low\_LGV). Shaded areas represent the 95% confidence intervals calculated by Cox analysis.

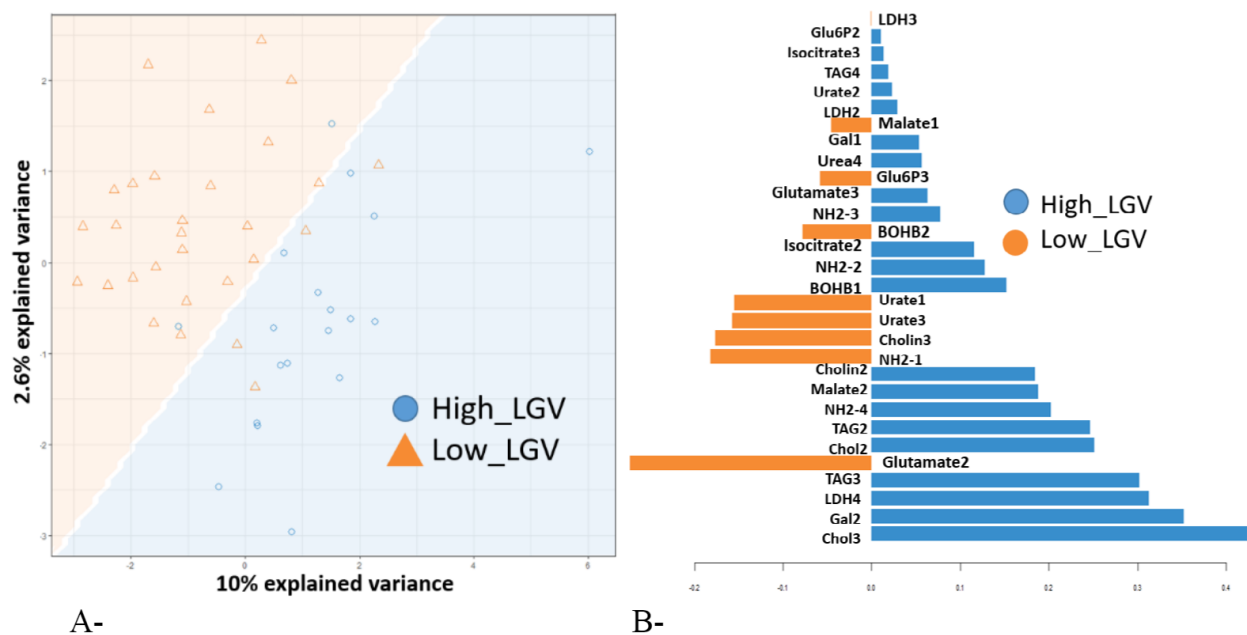
**Profiling of milk metabolites upon underfeeding challenge.** Using functional principal component analysis, between 2 and 4 components were required to explain at least 80% of variation resulting in 50 variables for the Sparse PLS-DA (named Chol1, Chol2 and Chol3 for variables describing cholesterol profiles). Figure 2 details the construction of the fPCA for Glu.



**Figure 2.** Functional principal component analysis results for one milk metabolite (concentration of milk free glucose) through the underfeeding challenge. (A) Individual raw data, each line represents 1 goat. Colors represent lines. (B) Fraction of variance explained by the first 3 PCA components. (C) Estimation of the mean curve by functional smoothing. (D) Underlying Eigenfunctions.



**Discriminating longevity goat lines with milk metabolites.** The optimal number of components in the sPLS-DA was 3. The lasso penalization selected 30, 2 and 20 variables for components 1, 2 and 3, respectively. The balanced error rate estimated for the model was 30.2% (respectively 30.0 and 30.3 for low\_LGV and high\_LGV lines). As shown in Figure 3 the most discriminating parameters between lines were Chol3, Gal2, LDH4, and TAG3. These results indicate that differences in functional longevity, which are seemingly due to differences in resilience, can be detected from milk metabolite responses to a short-term underfeeding challenge. Further, this preliminary analysis suggests that the physiological mechanisms underpinning differences in resilience are related in part to lipid metabolism.



**Figure 3.** (A) Sample plot from the sPLS-DA applied to the fPCscores of milk metabolites to discriminate lines of goats for functional longevity. (B) Loading plot from the sPLS-DA. Colors indicates the line in which the median is maximum for each fPCscore.

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