Title of Contribution

Resilience of preimplantation bovine embryos to the availability of energy substrates

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Abstract

Exposure to metabolic stress during fetal life increases the susceptibility to metabolic diseases in adulthood. This notion is supported by epidemiological and experimental evidences that led to the theorization of the Developmental Origins of Health and Disease. The adaptive mechanisms the embryo/fetus puts in place to cope with intra-uterine stressors is defined developmental plasticity and entails the capacity of one genotype to generate several phenotypes in response to a different environment. To capture the main molecular events of developmental plasticity, we monitored the gene expression of bovine blastocysts exposed in vitro to a mild metabolic challenge. With preliminary experiments we standardized the experimental model to remove sources of variability, such as serum, embryos of different sex, and blastocyst at different stages. Then metabolic challenges were administered by varying the content in energetic substrates of the culture medium. Three energetic levels, containing 0.5, 1.0, and 1.5-fold increase in energetic substrates, were selected based on the absence of apparent changes in preimplantation embryo development, evaluated by blastocyst rate, distribution of blastocyst morphology (early, expanded, hatch-ed/ing), number of cells composing the blastocyst, and pattern of cell lineage specification. Genome-wide analysis revealed minimal differences in gene expression among the three groups, likely exposing key regulatory genes whose differential expression allowed the adaptation to the changing metabolic environment. Two distinct expression patterns were observed for these genes: progressive upregulation and progressive downregulation along with the increasing energetic availability. The lack of substantial differences seems in line with the general observation that offspring born after a mild intra-uterine exposure to metabolic stress have normal physiological and biochemical parameters until later in life, while a generalized disruption of gene expression would probably impact embryo/fetal/early post-natal life rather than induce a late onset of the disease. Nevertheless, if metabolic stress experienced during preimplantation development were to commit a late phenotype, some kind of mark shall be established at this stage. A possible answer to this question came from the analysis of transcript isoforms. Using a specific bioinformatic pipeline, the presence of two or more transcript isoforms of genes related to epigenetic changes and nuclear reprogramming were detected, indicating that, even in absence of obvious changes in gene expression, the metabolic challenge induced biological effects that can be epigenetically encoded in the embryo. As a proof of concept, acetylation of histone proteins increased when the energetic substrates were higher.

These findings shed light on the mechanisms at the onset of developmental plasticity, whereby the activation/repression of few key genes and usage of transcript isoforms confer resilience to metabolic stressors and provide a direct link between changes in the availability of energetic substrates and epigenetic reprogramming.

Funded by: MUR PRIN2017, No. 20172N2WL3_002; Piano di Sostegno alla Ricerca UNIMI: Linea 2 – Azione A

Keywords
metabolism, blastocyst, epigenetic