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Inter-species comparison of Milk Fat Globule Membrane proteins highlights the molecular diversity of lactadherin

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Fat is present in milk as droplets of triglycerides surrounded by a complex membrane deriving from the mammary epithelial cell and called Milk Fat Globule Membrane (MFGM). In-depth proteomic studies have been published for bovine MFGM proteins (Reinhardt and Lippolis, 2006). However, to date, only sparse studies exist on MFGM proteins from non-cow milks. We have characterized MFGM proteins in goat, mare and camel milks and we have highlighted prominent differences across species, especially for lactadherin, a major protein of the Milk Fat Globule Membrane (Cebo et al., 2010; Cebo et al., in revision; Saadaoui et al., in preparation). Lactadherin is involved in a wide range of biological functions including apoptosis, mammary gland development and involution, sperm-egg interaction, angiogenesis, and maintenance of the intestinal epithelium (Raymond et al., 2009). Multiple forms of lactadherin have been identified in mammals. A truncated 30-kDa protein consisting in the C-terminal factor V/VIII-like domain of lactadherin has been characterized in humans (Giuffrida et al., 1998). Two alternative splicing variants were shown to be expressed in mice mammary tissue. The variant predominantly expressed during lactation is longer with an additional 37-amino-acid stretch, multiply O-glycosylated, connecting EGF-like and factor VIII-like domains (Oshima et al., 1999). We have recently shown that lactadherin from goat milk appears as a single polypeptide chain whereas two polypeptide chains are easily identified in cattle by mass spectrometry. Lactadherin from mare's milk consists in three polypeptide chains with apparent molecular weight ranging in size between 48 kDa and 62 kDa. Both post-transcriptional (*i.e.* splice variants) and post-translational (*i.e.* glycosylation variants) events have been identified in the horse species. Two major polypeptides have been identified for lactadherin in camel milk. Expression of lactadherin is thus species-dependent, therefore questioning about of the precise function of these different isoforms in mammary gland biology across species. Multiple forms of lactadherin are also involved in severe pathologies including breast cancer, Alzheimer disease and systemic lupus erythematosus thus highlighting the need to better understand molecular mechanisms regulating lactadherin expression in mammals.

Keywords: Milk Fat Globule Membrane, lactadherin, alternative splicing, glycosylation.