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Stem cells from foetal adnexa and fluid in domestic animals: an update on their features and clinical application.

Running Title: MSCs from foetal adnexa in domestic animals

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Summary

Over the past decade stem cell research has emerged as an area of major interest for its potential in regenerative medicine applications. This is in constant need of new cell sources to conceive regenerative medicine approaches for diseases that are still without therapy. Scientists drew the attention toward alternative sources such as foetal adnexa and fluid, since these sources possess many advantages: first of all, cells can be extracted from discarded foetal material and it is noninvasive for the patient and inexpensive, secondly abundant stem cells can be obtained and finally, these stem cell sources are free from ethical considerations. Cells derived from foetal adnexa and fluid preserve some of the characteristics of the primitive embryonic layers from which they originate. Many studies have demonstrated the differentiation potential in vitro and in vivo toward mesenchymal and non-mesenchymal cell types; in addition the immune-modulatory properties make these cells a good candidate for allo- and xenotransplantation. Naturally occurring diseases in domestic animals can be more ideal as disease model of human genetic and acquired diseases and could help to define the potential therapeutic use efficiency and safety of stem cells therapies. This review offers an update on the state of the art of characterization of domestic animals MSCs derived from foetal adnexa and fluid and on the latest findings in pre-clinical or clinical setting of the stem cell populations isolated from these sources.

Key words: Amniotic fluid, Amniotic Membrane, Umbilical cord blood, Wharton's Jelly, Mesenchymal Stem Cells

Introduction

A stem cell is an undifferentiated cell capable of differentiating into specialized cells and to originate other stem cells. In mammals, there are three types of stem cells (SCs): embryonic stem cells (ESCs), foetal stem cells, and adult stem cells. ESCs derive from the inner cell mass (ICM) of a blastocyst. They are pluripotent but highly tumorigenic after transplantation. Foetal stem cells are distinguished into two types: foetal proper stem cells (from the tissue of the fetus), and extra-embryonic foetal stem cells (from extra-embryonic membranes). Adult SCs are multipotent cells, designate to tissue repairing, and they are present in almost all adult tissues.

Mesenchymal stem cells (MSCs) are a population of multipotent stem cells that meet the following criteria: 1) plastic-adherence when maintained in standard culture conditions; 2) expression of CD105, CD73 and CD90, and lack of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules; 3) differentiation to osteoblasts, adipocytes and chondroblasts in vitro (Dominici et al. 2006).

Since these properties, MSCs offer a great chance for cell-based therapies and tissue engineering applications. The effective management of companion animals, such as dog, cat or horse, requires sophisticated new treatments and preventive strategies. This, combined with their role as models for human diseases, led to an increase in the number of research focused on isolation and clinical use of MSCs in these animals.

Bone marrow (BM) is the common source of autologous MSCs for clinical applications in veterinary medicine. Alternatively, adipose tissue-derived MSCs can be used, since they have a higher proliferation potential. Anyway, for both sources, an invasive procedure is required and there is a large variability in the cell yield related to the donor (Colleoni et al. 2009).

Placental tissues and foetal fluids represent a source of cells for regenerative medicine, and are readily available and easily procured without invasive procedures. MSCs from foetal

fluids and adnexa are defined as an intermediate between ESCs and adult SCs, due to the preservation of some characteristics typical of the primitive native layers. Among foetal adnexal tissues, the major sources of MSCs are amnion, amniotic fluid, umbilical cord and umbilical cord blood. These cells can be obtained in large numbers without risks for donors and cryopreserved for future use in regenerative veterinary medicine.

The markers required for defining a MSC were determined for human cells, and the lack of specific antibodies for different animal species lead to a great variability of approaches and results for molecular characterization of animal MSCs. The aim of this review is to provide an overview of the advances in characterization and clinical applications of domestic animal MSCs derived from foetal adnexa and fluid.

Developmental biology of foetal adnexa and amniotic fluid

Extra-embryonic or foetal membranes are structures that develop from the zygote, do not form part of the embryo itself, and are of functional importance only in embryonic life. At the end of cleavage, the blastocysts, enclosed within the zona pellucida, consists of an ICM and a trophoblastic layer. During the second week of development, hatched blastocyst leaves its confined space and elongates. In particular this process involves the trophoblast, and, partially, the inner endodermal lining. The head and tail of growing embryo, progressively, push deeper in to the trophoblast, which become lined by a layer of somatic mesoderm forming the extra-embryonic somatopleure (McGeady et al. 2006). The outer somatopleure membrane forms chorion, while the inner somatopleure membrane, attached to the embryos at umbilicus, forms amnion. Due to its early development, amnion could be a reservoir of pluripotent stem cells, derived from the contiguity of embryonic epiblast, even at full term pregnancy. Amnion is a thin, tough, membranous and fluid-filled sac which surrounds and protects the embryo and then the foetus (McGeady et al. 2006). When first formed, it is in

contact with the embryo's body, but, after few weeks of pregnancy, fluid begins to accumulate within it. This fluid increases in quantity relatively rapidly up to mid-pregnancy and then gradually decreases. In early pregnancy, the composition of amniotic fluid and plasma are similar and may be considered a dialysate of the maternal or foetal extracellular fluid. Later in gestation, when the foetus urethra becomes patent, foetal urine passes in amniotic cavity. Amniotic fluid (AF) contains less than 2% of solids, consisting of urea and other extractives, inorganic salts, a small amount of protein, a trace of sugar and multiple cell types from embryonic and extra-embryonic tissues (Gosden 1983).

With the progress of gestation, the embryo sinks into the amniotic membrane (AM), which wraps the mesoblastic axis in which allantois and umbilical vessels developed, giving rise to the umbilical cord (UC) (Barone 1994). Based on structural and functional studies, at least four distinctive zones are now recognized in the UC: surface amniotic epithelium, subamniotic stroma, perivascular stroma, vessels. All together these structures are called umbilical cord matrix (UCM). The connective tissue included between subamnion and perivascular regions consists of mucous, mesenchymal connective tissue, and it is called Wharton's jelly (WJ). It contains a very low number of cells and a high amount of extracellular matrix components, such as collagen, hyaluronic acid and proteoglycans (Sobolewski et al. 1997). These substances make this tissue highly hydrated and resistant to extension and compression evoked by foetal movements and uterine contraction. Stromal cells of WJ, previously described as myofibroblast (Takechi et al. 1993), have properties of potentially multipotent SCs (Mitchell et al. 2003).

Amniotic membrane

After mechanically separating amnion from allantois, as in human medicine, it is possible to harvest two cellular types, amniotic epithelial (AECs) or mesenchymal cells (AMSCs). AECs

have a typical polygonal morphology while AMSCs are fibroblast-like. Both AMSCs and AECs from different species have been investigated for proliferative potential, differentiation ability, and phenotypically characterized.

AECs showed similar patterns to AMSCs in the sheep (Gloria et al. 2010; Mauro et al. 2010; Mattioli et al. 2012), but the latter were superior in promoting interbody fusion in induced anterior cervical discectomy after allogenic implantation combined with bone grafts (Goldschlager et al. 2011). AECs phenotype, methylation status, immunomodulatory and stemness properties are affected by gestational age (Barboni et al. 2014). In the horse (Lange-Consiglio et al. 2012) and in the bovine (Corradetti et al., 2013), AECs showed a lower number of doublings compared to AMSCs but the same phenotype and plasticity at differentiation. Feline AECs were fully characterized and were able to differentiate into adipogenic, chondrogenic, osteogenic and neurogenic lineages (Rutigliano et al. 2013). Porcine AECs were successfully used for construction of tissue-engineered cornea (Luo et al. 2013).

Focusing on MSCs, they express pluripotency and mesenchymal markers, have a multi-lineage differentiation potential and possess a privileged immunogenic status related to the low expression or even absent levels of MHC I and MHC II (data are summarized in Table 1). AMSCs were capable of inhibiting peripheral blood mononuclear cell proliferation after allogenic stimulation either when co-cultured in cell-to-cell contact or when separated by a transwell membrane (Lange-Consiglio et al. 2013b). Furthermore, it was demonstrated that AMSCs possess nonteratogenicity 4 weeks post injection into immunodeficient mice (Vidane et al. 2014).

Comparing results from different species, among pluripotency markers, a difference was found for NANOG expression. While in the horse (Violini et al. 2012) and buffalo (Dev et al. 2012; Mann et al. 2013) AMSCs expressed NANOG at RT-PCR, canine AMSCs were

151 negative (Filioli Uranio et al. 2011, 2014). Anyway, Park et al. (2012) could quantified it in
152 canine AMSCs using qPCR.
153 Mesenchymal markers were expressed in all species while haematopoietic markers were not
154 found. In the horse, CD34 was not expressed in early stages of culture, but began to be
155 expressed at later passages (P5) (Lange-Consiglio et al. 2013a). By the way, the consensus
156 about absence of CD34 expression on MSCs has been challenged. The CD34 expression
157 status in haematopoietic and MSCs appears to depend on the environment, and can change
158 from positive to negative, and vice versa (Lin et al. 2012).
159 Karyotype of cultured AMSCs was confirmed to be stable in the dog (Filioli Uranio et al.
160 2011, 2014), buffalo (Dev et al. 2012c; Mann et al. 2013) and horse (Seo et al. 2013). In the
161 dog, a high telomerase activity was found (Filioli Uranio et al. 2011). Telomerase activity and
162 telomere maintenance characterize all cells with self-renewal capability, such as ESCs, MSCs,
163 and most cancer cells (Colosimo et al. 2013a).
164
165 **Amniotic fluid**

166 In the veterinary field, as in the human, AF contains a heterogeneous population of cells:
167 cuboidal epitheloid (E-cells), round (R-cells) and spindle-shaped fibroblastic (F-cells) cells.
168 E-cells probably derive from foetal skin and urine and they are lost during the first passages
169 of culture; R-cells are supposed to originate from foetal membranes and trophoblasts; F-cells
170 are generated from mesenchymal tissues and are supposed to be the MSC population of the
171 AF (Klemmt et al. 2011). In domestic animals, the prevalent cell population that persist
172 during culture is the F-type, except for one study on porcine AFMSCs (Sartore et al. 2005)
173 and one on bovine AFMSCs (Rossi et al. 2014), where both F-cells and R-cells persist
174 through passages. Other groups, that studied bovine AF cell populations (Corradetti et al.
175 2013; Gao et al. 2014; da Cunha et al. 2014), found R-cells only at the very first passages,
176 maybe due to the addition in the culture medium of growth factors like EGF and bFGF.

AFMSCs generally express MSC markers and mesodermal markers like Vimentin and α-Smooth Muscle Actin (αSMA) and are negative for haematopoietic markers (Table 2). In the horse, expression of CD73 is controversy. Positivity was found only for AD2 clone, while clone 5F/B9 did not cross-react (Gulati et al. 2013). Anyway, for AD2 clone cross-reactivity was not found in equine (Iacono et al. 2012a) and also in feline (Iacono et al. 2012b) and bovine AFMSCs (Rossi et al. 2014). Like AMSCs, also AFMSCs express pluripotency markers and only in one study in the bovine (Rossi et al. 2014) expression of OCT4, NANOG and SOX2 was not found.

Different authors verified that AFMSCs show telomerase activity and that telomere length is not affected by culture conditions (Filioli Uranio et al. 2011; Colosimo et al. 2013a), such as karyotype (Filioli Uranio et al. 2011; Dev et al. 2012a; Dev et al. 2012b; Colosimo et al. 2013b; Weber et al. 2013; da Cunha et al. 2014).

Umbilical cord blood (UCB)

In human medicine, the use of UCB as a source of MSCs can be traced back to 2000: in this year Erices et al. showed that UCB cells were able to give rise to two types of adherent cells, one of which expressed antigens typical of MSCs. Also in veterinary medicine cells with characteristics similar to human UCBMSCSs have been isolated in different species (Table 3). Usually, an isolation rate of fibroblast-like, spindle-shaped cells, similar to human, between 50 and 70% is reported (Koch et al. 2007; Iacono et al. 2012a; Mohanty et al. 2014), except for feline UCB where cells at P0 comprised a heterogeneous population, including fibroblast-like, spindle-shaped, and small round morphologies (Jin et al. 2008). Reported data may be due to the limited number of MSCs in UCB as well as suboptimal isolation and expansion conditions. In horses was demonstrated that samples cultured at 5% O_2 proliferated rapidly to the desired cell number. The effect of mild hypoxia may be attributable in part to the

induction of signaling pathways but also to a decrease in survival of contaminating leukocytes in UCB, thus increasing the isolation rate up to 80% (Schuh et al. 2009). Furthermore, particularly in equine species, the UCB recovered volume is often low, because of a wide spread belief that the mare continues to pass blood to the foal through the umbilicus immediately post foaling (Rossdale 1958). However, using Doppler ultrasound, Doarn (1985) showed that blood flow through the cord ceases within few minutes following delivery. All authors reported that UCBMSCs cells from domestic animals sources were positive for CD44 (Table 3), an antigen expressed by a variety of cells types, not part of the ISCT MSC definition (Dominici et al. 2006). Given its constant expression and considering the difficulty in UCBMSCs isolation, sorting of CD44+ cells prior to plastic adherence isolation could lead to more homogenous populations in domestic animals (Paebst et al. 2014). A variability of the other MSCs marker expression exists particularly for CD73. Similarly to AFMSCs, in the horse only Mohanty et al. (2014) showed that UCBMSCs expressed CD73, both with RT-PCR and flow cytometry. Authors explained their finding with the use of different CD73 clones (5F/B9), compared with a previous study reporting its negative expression (De Schauwer et al. 2012; 10fl clone). However, Mohanty's research group stated that equine AFMSCs reacted with AD2 clone, but not with 5F/B9 clone (Gulati et al. 2013), showing opposing results for the same species. Anyway, differences in the culture medium, such as the content of FBS, the timeframe of plastic-adherent culture and the cell harvesting technique could influence the cell characteristics (Paebst et al. 2014).

UCBMSCs from different species possess an intermediate phenotype that more closely resembles ES cells: Tra1-60, Tra1-81 and Oct4 are present (Reed et al. 2008; Seo et al. 2009; Raoufi et al. 2011; Mohanty et al. 2014), but conflicting data are reported for Nanog and Sox2 (Reed et al. 2008; Mohanty et al. 2014), particularly in the horse.

Umbilical Cord

UC is routinely discarded at parturition and its extracorporeal nature facilitates isolation by eliminating the invasive and discomfort extraction procedures as well as patient risks that attend adult stem cell isolation. Most significantly, the comparatively large volume of UC and ease of physical manipulation theoretically increase the number of stem cells that can be extracted, which make it possible to get substantial number of cells in several passages without need of long term culture and extensive expansion ex vivo. Probably due to the possible absence of this structure at birth, because of reduction of the water and substances content towards the end of pregnancy, different authors, particularly in veterinary medicine, named interchangeably WJ or UCM. Due to this reason, in Table 4, we reported data regarding WJ and UCM MSCs together. Usually, spindle-shaped cells have been isolated; however few authors described a heterogeneous cell population (fusiform or spindle form and small round cells with large and prominent nucleus), from porcine and caprine UC, characterized by a plateau or a stationary phase (Mitchell et al. 2003; Babaei et al. 2008). In these species, such as in canine (Filioli Uranio et al. 2011) and bovine (Cardoso et al. 2012), UC cells expressed high levels of telomerase activity, and this phenomenon could explain the long term of cell culture observed by the authors. Moreover, tissue culture procedure does not alter chromosomal organization (Filioli Uranio et al. 2011; Cardoso et al. 2012; da Cunha et al. 2014). As reported above, also cell isolated from UC are negative for hematopoietic markers and express a number of antigens associated with adult MSCs (Table 4). Conflicting data are reported regarding their expression of embryonic markers. Cells from porcine, bubaline and equine UC resulted positive for pluripotency genes OCT4, NANOG, SOX2 at different culture passages (Mitchell et al. 2003; Carlin et al. 2006; Hoynowsky et al. 2007; Singh et al. 2013; Sreekumar et al. 2014). In canine, all authors agree that during in vitro passages cells lost OCT4 expression. However, while Lee et al. (2013a) stated that expression of NANOG and SOX2 is negatively correlated with the number of passages but is always

present, most recently Filioli Uranio et al. (2014) showed that NANOG gene is present only in cells recovered at late gestational age. This discrepancy is likely due to different culture conditions and to different selection of cord tissue to be processed. The immature cells that retain the ability to proliferate were located close to the amniotic surface, whereas highly differentiated, non-proliferating fibroblasts were located in closer proximity to the umbilical vessels (Nanaev et al. 1997).

Clinical Applications

Clinical application of foetal MSCs in domestic animals had an increase in the last five years. The majority of the studies are on AFMSCs, mainly used in animal-model diseases (heart, diaphragm, trachea and tendon induced injuries in different species) (Table 5). Among tissue-engineering studies in the sheep, diaphragmatic repair with a mesenchymal amniocyte-based engineered tendon led to improved structural outcomes when compared with equivalent fetal myoblast-based and acellular graft (Kunisaki et al. 2006c). Investigating the ability of AFMSCs for phenotypic conversion to vascular cells and cardiomyocytes (CM) when autotransplanted in a porcine model acute ischemic myocardium (AMI), MSCs were able to transdifferentiate to cells of vascular cell lineages but not to CM. Thus, porcine AFMSCs may require further ex vivo re-programming to be suitable for therapeutic use in AMI (Sartore et al. 2005). On the other hand, intramuscular injection of porcine AFMSCs reduced scar size and preserved heart function after induced myocardial infarction in mice (Peng et al. 2014). Only in the horse AFMSCs were used, combined with PRP (plateled rich plasma), to treat spontaneous decubitus ulcers (Iacono et al. 2012c). When comparing different treatments (aloe gel, PRP alone, MSCs+PRP), mean regression of ulcer treated with MSCs+PRP was higher than others.

Despites animal UC cells molecular characterization, in vitro differentiation and their immunosuppressive effects on T-cells in vitro (Cardoso et al. 2012), there are sparse literatures documenting their therapeutic applications (Table 5). Equine UCBMSCs were successfully used as allogenic therapy in race-horses with spontaneous tendon lesions (Kang et al. 2013; Van Loon et al. 2014). Canine UCBMSCs and WJMSCs were mainly applied to treat induced spinal cord injuries or bone defects. Dog WJMSCs can replace adult MSCs in clinical bone engineering procedures (Kang et al. 2012) and promote functional recovery in spinal cord injured dogs after allogenic transplantation (Ryu et al. 2012). Caprine WJMSCs allogenic (Azari et al. 2011) and xenogenic transplantation (Pratheesh et al. 2014) in a rabbit model, could be successfully performed for treating induced skin wounds. In not-treated wounds, incomplete re-epithelialization and thick granulation tissue were observed, whereas, in treated wounds intact skin with complete re-epithelialization, no inflammation, and thin granulation tissue were seen. Furthermore, in both studies, histomorphological evaluation demonstrated better epithelization, lower neovascularisation, and denser collagen fibres in treated wounds.

Although implantation of human AMSCs into animals resulted in successful and persistent engraftment in multiple organs and tissues (Lindenmair et al. 2012), their application in veterinary medicine are still limited (Table 5). In fact, except for a study to enhance cervical interbody fusion in an ovine model (Goldschlader et al. 2011) and histological and functional improvement after transplantation in a porcine model of chronic myocardial ischemia (Kimura et al. 2012), AMSCs were only applied in equine spontaneous tendon injuries. Allogenic transplantation resulted in a quick reduction in tendon size and ultrasonographic cross-sectional area (Lange-Consiglio et al. 2012) and the re-injury rate was lower compared to autologous BMMSCs transplantation (Lange-Consiglio et al. 2013c). The hypothesis of a paracrine mechanism of tendon repair when AMSCs are injected was confirmed in vivo; when horse tendon injuries were treated with conditioned medium, a lower rate of re-injuries

was observed compared to untreated animals (Lange-Consiglio et al. 2013b). AMSCs and their conditioned medium were recently considered candidates for equine uterine regenerative therapy, due to their ability to increase in vitro endometrial cell proliferation rate (Corradetti et al. 2014). So far, AMSCs are promising not only for cell-based therapies, but also for novel therapeutic biological cell-free products.

Conclusion

Altogether, these studies offer authoritative views on markers expression and therapeutic potential of MSCs from foetal tissues and fluids in domestic animals. These sources are easily available and relatively abundant, so MSCs may have an attraction compared to other established SCs in different clinical approaches. Anyway, more clinical applications are needed to fully understand their properties and to establish the future clinical use in the treatment of various diseases.

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685

689 **Table 1**. AMSCs characterization.

Species	Phenotype	*In vitro* differentiation	Ref.
Sheep	**ICC**: Oct4+,TERT+	Osteogenic, myogenic	(Mauro et al. 2010)
Horse	**FCA**: CD44+,CD90+,CD14+,CD45+,CD29-,MHCI-,MHCII- **ICC**: cKit+,Oct4+,CD105+	Adipogenic, chondrogenic, osteogenic	(Coli et al. 2011)
	RT-PCR: OCT4+,SOX2+,NANOG+,CD105+,CD34-	Adipogenic, chondrogenic, osteogenic	(Violini et al. 2012)
	ICC: Tra1-60+,SSEA3+,SSEA4+,Oct4+ **RT-PCR**: CD29+,CD105+,CD44+,CD166+,CD34-, MHCI+,MHCII-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Lange-Consiglio et al. 2012)
	FCA: CD44+,CD90+,CD105+,CD19-,CD20-,CD28-,CD31-, CD34-,CD38-,CD41a-,CD62L-,CD62P-,CD200-	Adipogenic, chondrogenic, osteogenic	(Seo et al. 2013)
	AP+ **ICC**: Tra1-60+, SSEA4+,Oct4+ **RT-PCR**: CD29+,CD105+,CD44+,CD166+,CD34-, MHCI+,MHCII-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Lange-Consiglio et al. 2013a)
	FCA: Oct4+,SSEA4+,cMyc+,CD34- **RT-PCR:** CD29+,CD44+, CD166+, CD105+, CD34- MHCI+,MHCII-		(Corradetti et al. 2014)
Dog	**RT-PCR**: OCT4+,NANOG-,CD44+,CD184+,CD29+,CD34-,CD45-, DLA79-,DLA88-,DLA-DRA1-,DLA-DQA1-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Filioli Uranio et al. 2011)
	FCA: CD90+,CD105+,CD3-,CD11c-,CD28-,CD34-,CD38-, CD41a-,CD45-,CD62L- **qPCR**: OCT4+,SOX2+,NANOG+,KLF4+	Adipogenic, chondrogenic, osteogenic, neurogenic	(Park et al. 2012)

	RT-PCR: OCT4+,NANOG-,CD29+,CD44+,CD184+,CD34-, CD45-,DLA79-,DLA88-,DLA-DRA1-,DLA-DQA1-	Osteogenic, neurogenic	(Filioli Uranio et al. 2014)
Cat	**FCA**: CD44+,CD90+,CD105+,CD14-,CD34-,CD45-,CD73-	Adipogenic, chondrogenic, osteogenic	(Iacono et al. 2012b)
	FCA: CD73+,CD90+,CD34±,CD45-,CD79-	Adipogenic, chondrogenic, osteogenic	(Vidane et al. 2014)
Buffalo	**AP**+ **RT-PCR**: OCT4+,SOX2+,NANOG+,AP+,SCF+,NESTIN+		(Dev et al. 2012c)
	AP+ **RT-PCR**: OCT4+,SOX2+,NANOG+	Osteogenic	(Mann et al. 2013)
Bovine	**RT-PCR**: OCT4+,Myc+,CD44+,CD166+,CD73+,CD29+, CD105-,CD45-,CD14-,CD34-,MHCI+,MHCII-	Adipogenic, chondrogenic, neurogenic	(Corradetti et al. 2013)

690 +: positive, -: negative; ±: weakly positive; ICC: immunocytochemistry.

691 **Table 2**. AFMSCs characterization.

Species	Phenotype	*In vitro* differentiation	Ref.
Sheep	**ICC:** FSP+,CD31-,Vimentin+,αSMA+,Desmin-,CK8+,CK18+		(Kaviani et al. 2001)
	ICC: Vimentin+,CK8+,CK18+,CD31-	Chondrogenic	(Kunisaki et al. 2006a)
		Chondrogenic	(Kunisaki et al. 2006b)
	FCA: CD29+,CD44+,CD90±,CD105±,CD31-	Adipogenic, osteogenic	(Kunisaki et al. 2007)
	ICC: Oct4+,TERT+	Osteogenic, myogenic	(Mauro et al. 2010)
	FCA: CD44+,CD58+,CD166+,CD14-,CD31-,CD45-	Adipogenic, osteogenic	(Shaw et al. 2011)
	FCA: CD29+,CD44+,CD105+,CD166+,CD31-		(Gray et al. 2012)
	ICC: SSEA4+,STRO4+,CD29+,CD44+,CD166+ **RT-PCR**: OCT4+,NANOG+,SOX2+		(Weber et al. 2012)
	ICC: TERT+,Sox2+,Nanog+ **semiqPCR**: TERT+,NANOG+,SOX2±,OCT4±	Osteogenic	(Colosimo et al. 2013a)
	FCA: Sox2+,Nanog+,TERT+,CD166+,CD29±,CD58±,CD14-,CD31-,CD45-,c-Kit- **ICC**: Sox2+,Nanog+,TERT+,c-Kit-	Adipogenic, osteogenic, tenogenic	(Colosimo et al. 2013b)
	FCA: TERT+,Oct3/4+,Nanog+,Sox2+,CD29+,CD58+,CD90+,CD166±,CD14-,CD31-,CD45-,CD49f-,CD117-,HLA-ABC+, HLA-DR-	Osteogenic	(Di Tomo et al. 2013)
	FCA: CD44+,CD166+,CD29+,STRO4+ **ICC**: CD29+,CD44+,STRO4+,CD166±,CD11b-	Chondrogenic, osteogenic, endothelial, myogenic/myofibroblasts	(Weber et al. 2013)

	,Vimentin+,αSMA±,Desmin± **qPCR**: NANOG+,STAT3+		
Swine	**ICC**: SSEA4±,Oct4±,CD90+,Vimentin+,vWf+,SM22+,VE-Cadherin±,αSMA±,CD31±,CD105-,CD117-,CD34-,CD45-,Sca-1-,CardiacTnI-		(Sartore et al. 2005)
	RT-PCR: OCT4+,SOX2+,THY+	Adipogenic, osteogenic, neurogenic, myogenic, endothelial	(Zheng et al. 2009)
	RT-PCR: OCT4+,SOX2+,THY+	Neurogenic	(Zheng et al. 2010)
	FCA: CD44+,CD166+,CD34-,CD45-,CD54- **ICC**: Oct4+,Nanog+,Tra1-60+,Tra1-81+,SSEA4+,SSEA1- **RT-PCR**: CD90+,CD117+,HLA-ABC+,CD45-	Adipogenic, neurogenic, cardiomyogenic; Multilineage-differentiation through EBs	(Chen et al. 2011)
	FCA: CD44+,CD90+,CD31-,CD4a-		(Peng et al. 2014)
Horse	**ICC**: Oct4+,SSEA4+,Tra1-60± **RT-PCR**: CD29+,CD44+,CD105+,CD34-,ELA-ABC+,ELA-DR-	Adipogenic, chondrogenic, osteogenic	(Lovati et al. 2011)
	FCA: CD44+,CD90+,CD105+,CD14-,CD34-,CD45-,CD73-	Adipogenic, chondrogenic, osteogenic	(Iacono et al. 2012a)
		Adipogenic, chondrogenic, osteogenic	(Iacono et al. 2012c)
	AP+ **FCA**: CD29+,CD44+,CD90+,CD73(clone 5F/B9)-,CD73(clone AD2)+,CD34-,CD45- **ICC**: CD73+,CD90+,CD34-,CD45- **RT-PCR**: CD73+,CD90+,CD105+,CD14-,CD34-,CD45-	Adipogenic, chondrogenic, osteogenic, tenogenic	(Gulati et al. 2013)

Dog	**RT-PCR**: OCT4+,NANOG-,CD44+,CD184-,CD29-,CD34-,CD45-,DLA79+,DLA-DRA1+,DLA-DQA1-,DLA 88-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Filioli Uranio et al. 2011)
	ICC: Vimentin+, Nestin+, CK18+	Adipogenic, chondrogenic, osteogenic, neurogenic	(Fernandes et al. 2012)
	FCA: CD29+,CD44+,CD90+,CD34- **ICC**: Oct4+,Nanog+,Sox2+,CD29+,CD44+,CD90+,CD34- **RT-PCR**: OCT4+,NANOG+,SOX2+	Adipogenic, chondrogenic, osteogenic, hepatogenic	(Choi et al. 2013)
		Neurogenic	(Kim et al. 2014)
Cat	**FCA**: CD44+,CD90+,CD105+,CD34±,CD14-,CD45-,CD73-	Adipogenic, chondrogenic, osteogenic	(Iacono et al. 2012b)
Buffalo	**AP**+ **RT-PCR**: OCT4+,NESTIN+,FGF5+		(Dev et al. 2012a)
	AP+ **RT-PCR**:OCT4+,NANOG+,SOX2+,AP+,SCF+,CyclinA+,NESTIN+,FGF5+	Neurogenic	(Dev et al. 2012b)
	AP+ **qPCR**: OCT4+,NANOG+,SOX2+		(Yadav et al. 2012)
Caprine	**FCA**: Nanog+,Sox2+ **ICC**: Oct4+,Nanog+,Sox2+,SSEA4+,SSEA1+ **RT-PCR**: CD73+,CD90+,CD105+,CD34-	Adipogenic, chondrogenic, osteogenic	(Pratheesh et al. 2013)

Bovine	**RT-PCR**: OCT4+,MYC+,CD29+,CD44+,CD73+,CD166+,CD14-,CD34-,CD45-,CD105-,CD117+,MHCI+,MHCII-	Adipogenic, chondrogenic, neurogenic	(Corradetti et al. 2013)
	ICC: Oct4+,CD29+,CD44+,CD71+,CD34- **RT-PCR**: OCT4+,CD29+,CD44+,CD73+,CD166+,CD34-,CD45-	Adipogenic, chondrogenic, neurogenic	(Gao et al. 2014)
	FCA: CD34+,CD44+,CD90+,CD105+,CD14- **ICC**: Oct4-,SSEA4±,αSMA+,Vimentin+,N-Cadherin+,E-Cadherin-,CK- **qPCR:** OCT4-,NANOG-,SOX2-	Adipogenic, chondrogenic, osteogenic	(Rossi et al. 2014)

692 +: positive, -: negative; ±: weakly positive; ICC: immunocytochemistry.

693

694 **Table 3**. UCBMSCs characterization.

Species	Phenotype	*In vitro* differentiation	Ref.
Sheep		Chondrogenic	(Fuchs et al. 2005)
		Adipogenic, chondrogenic, osteogenic	(Jager et al. 2006)
	FCA: CD44+,CD38-,CD45-,CD41/61-		(Fadel et al. 2011)
Horse		Adipogenic, chondrogenic, osteogenic	(Koch et al. 2007)
	ICC: Oct4-,SSEA1-,SSEA3-,SSEA4-,Tra1-60-,Tra1-81-,AP+,CD29+,CD44+,CD90+,CD14-,CD79α-,Coll I+,Coll II+,Coll III+,Coll IX/XI+,MHCI±,MHCII-	Adipogenic, chondrogenic, Osteogenic	(Guest et al. 2008)
	AP + **ICC**: Oct4+,Tra1-60+,Tra1-81+,SSEA1+,SSEA4±	Adipogenic, chondrogenic, hepatogenic, myogenic	(Reed and Johnson, 2008)
		Chondrogenic	(Berg et al. 2009)
	ICC: Vimentin±,αSMA±,CD18-,PanCK-,Factor VIII-,Osteonectin-,Osteocalcin-	Adipogenic, chondrogenic, osteogenic	(Schuh et al. 2009)
		Osteogenic	(Toupadakis et al. 2010)
		Osteogenic	(Figueroa et al. 2011)
	FCA: CD86-,MHCI-,MHCII-		(Carrade et al. 2011)
	FCA: CD29+,CD44+,CD90+,CD86-,MHCI+,MHCII-,F6B-		(Carrade et al. 2012)
	FCA: CD29+,CD44+,CD90+,CD79α-,MHCII-	Adipogenic, chondrogenic,	(De Shauwer et al. 2011)

		osteogenic	
	FCA and Confocal Microscopy: CD29+,CD44+,CD90+,MHCII-,CD105±,CD45-,CD73±,CD79α-,monocyte marker-	Adipogenic, chondrogenic, osteogenic	(De Shauwer et al. 2012)
		Adipogenic, chondrogenic, osteogenic	(Burk et al. 2013)
	FCA: CD29+,CD44+,CD73+,CD90+,CD105+,CD45-CD79α-,MHCI+,MHCII-,monocyte marker- **RT-qPCR**: CD40+,CD80±,CD86-,TGFβ+,HGF±,IDO-,TNFα-	Adipogenic, chondrogenic, osteogenic,	(De Shauwer et al. 2013)
	FCA: CD90+,CD105+,CD20-,CD28-,CD38-,CD62L-CD200-,CD31-,CD62P-,CD34-,CD41a-	Adipogenic, chondrogenic, osteogenic	(Kang et al. 2013)
	FCA: CD29+,CD44+,CD73+,CD90+,CD105+,CD45-CD79α-,MHCI+,MHCII-,monocyte marker- **qPCR**: CD40+,CD80+,CD86-,TGFβ+,HGF±,IDO-,TNFα-	Adipogenic, chondrogenic, osteogenic,	(De Schauwer et al. 2014)
	FCA: CD29+,CD44+,CD73+,CD90+,CD34-,CD45- **ICC**: CD73+,CD90+,CD34-,CD45- **RT-PCR**:OCT4+,NANOG+,SOX2+,CD73+,CD90+,CD105+,CD14-,CD34-,CD45-	Tenogenic	(Mohanty et al. 2014)
	FCA: CD29±,CD44+,CD73-,CD90-,CD105-,CD14-CD34-,CD45-,CD79α-,MHCII-		(Paebst et al. 2014)
Dog		Osteogenic	(Jang et al. 2008)
	FCA: Oct4+,CD29+,CD33+,CD44+,CD105+,CD184+,CD4-,CD8a-,CD10-,CD14-,CD24-,CD31-,CD34-,CD38-,CD41a-,CD45-,CD49b-,CD41/61-,CD62p,CD73-,CD90-,CD133-,HLA-	Chondrogenic, osteogenic, neurogenic	(Seo et al. 2009)

		DR-		
		FCA: CD44+,CD73+,CD90+,CD105+,CD14-,CD34-,CD45-	Osteogenic	(Kang et al. 2012)
	Swine	**ICC**: CD29+,CD49b+,CD105+,CD45-,CD133-,SCF+,LIF+,G-CSF+	Adipogenic, chondrogenic, osteogenic	(Kumar et al. 2007)
	Cat	**FCA**: CD9+,CD44+,CD18-,CD45- **ICC**: Vimentin+	Neurogenic	(Jin et al. 2008)
	Bovine	**RT-PCR**: OCT4+,CD73+	Adipogenic, chondrogenic, osteogenic	(Raoufi et al. 2011)

695 + :positive; - : negative; ± : weakly positive; ICC: immunocytochemistry

696 **Table 4**. WJMSCs and UCMMSCs characterization.

Species	Phenotype	*In vitro* differentiation	Ref.
Swine	**Immunoblotting**: c-kit+,αSMA+	Neurogenic	(Mitchell et al. 2003)
	AP+ **ICC:** Oct4+,Nanog+ **RT-PCR**: OCT4+,NANOG+,SOX2+ **qPCR**: OCT4+,NANOG+,SOX2+		(Carlin et al. 2006)
Horse	**FCA**: CD54+,CD90+,CD105+,CD146+,Oct4+,SSEA4+,c-kit+, SSEA3±,Tra1-60±,HLA-ABC-,HLA-1AG-,MHCII-	Adipogenic, chondrogenic, osteogenic	(Hoynowski et al. 2007)
	RT-PCR: Oct4+, Sox2+		(Cremonesi et al. 2008)
		Adipogenic, chondrogenic, osteogenic	(Passeri et al. 2009)
		Osteogenic	(Toupadakis et al. 2010)
	FCA: Oct4+,c-myc+,CD34-,CD105-,SSEA4-,SSEA3-,Tra1-60- **RT-PCR**: CD29+,CD44+,CD105+,CD166+,CD14-CD34-, MHCI+,MHCII-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Corradetti et al. 2011)
	RT-PCR: CD29+,CD44+,CD105+,CD166+,CD14-CD34-, MHCI+,MHCII-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Lange-Consiglio et al. 2011)
	RT-PCR: CD29+,CD44+,CD105+,CD34-,MHCI+,MHCII- **ICC**: Oct4+,SSEA4+,Tra1-60±	Adipogenic, chondrogenic, osteogenic	(Lovati et al. 2011)
	RT-PCR: CaSR+		(Martino et al. 2011)
	FCA: CD86-,MHCI-,MHCII-		(Carrade et al. 2011)

	FCA: CD29+,CD44+,CD90+,CD86-,MHCI+,MHCII-,F6B-		(Carrade et al. 2012)
		Adipogenic, chondrogenic, osteogenic	(Burk et al. 2013)
	FCA: CD29+,CD44+,CD90+,CD45-,CD73-,CD79α-,CD105-, MCHII-,Monocyte marker-		(De Schauwer et al. 2013)
	FCA: CD44+,CD90+,CD105+,CD34-,MHCII- **ICC:** MHCII-	Adipogenic, chondrogenic, osteogenic	(Barberini et al. 2014)
	FCA: CD29+,CD44+,CD73+,CD90+,CD105+,CD45-,CD79α- MHCI+,MHCII-,monocyte marker- **qPCR**: CD40+,CD80+,CD86-,TGFβ+,HGF±,IDO-TNFα-	Adipogenic, chondrogenic, osteogenic,	(De Schauwer et al. 2014)
	FCA: CD29+,CD44±,CD73-,CD90-,CD105-,CD14-,CD34-, CD45-,CD79α-,MHCII-		(Paebst et al. 2014)
		Chondrogenic	(Co et al. 2014)
Caprine	**AP**+ **RT-PCR:** NANOG-		(Babaei et al. 2008)
	AP+ **FCA:** CD44+,CD34- **ICC:** αSMA+		(Azari et al. 2011)
	FCA: STRO1+,CD73+,CD105+,CD34- **ICC:** STRO1+,CD73+,CD105+,CD34-	Adipogenic, chondrogenic, osteogenic	(Pratheesh et al. 2014)
Dog	**RT-PCR**: CD29+,CD44+,CD184+,OCT4+,CD34-,CD45-, DLA-DQA1-,DLA79-,DLA88-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Filioli Uranio et al. 2011)

	FCA: CD44+,CD73+,CD90+,CD105+,CD14-,CD34-,CD45-	Osteogenic	(Kang et al. 2012)
	FCA: CD44+,CD73+,CD90+,CD105+,CD14-,CD34-,CD45-	Adipogenic, osteogenic, neurogenic	(Ryu et al. 2012)
	FCA: CD90+,CD105+,CD11c-,CD34-,CD3-,CD45-,CD28-, CD38-,CD62L,CD41a-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Seo et al. 2012)
	RT-PCR: CD44+,CD54+,CD61+,CD80+,CD90+,CD105+	Chondrogenic	(Lee et al. 2013a)
	FCA: CD44+,CD90+,CD105+,CD184+,CD29-,CD33-,CD34-,CD45- **ICC**:Oct3/4+,Nanog+,Sox2+,SSEA4+,CD44+,CD90+,CD105+,CD184+ **RT-PCR**: OCT3/4+,NANOG+,SOX2+,CD44+,CD90+,CD105+, CD184+,CD29-,CD34-,CD45-	Adipogenic, chondrogenic, osteogenic, neurogenic	(Lee et al. 2013b)
	FCA: CD29+,CD44+,CD184+,OCT4+,CD34-,CD45-, DLA-DRA-,DLA-DQA1-,DLA79-,DLA88-	Osteogenic, neurogenic	(Filioli Uranio et al. 2014)
Bovine	**RT-PCR**: OCT4+,ITSN1+	Adipogenic, chondrogenic, osteogenic, neurogenic	(Cardoso et al. 2012a)
		Neurogenic	(Cardoso et al. 2012b)
Buffalo	**FCA:** CD29+,CD73+,CD90+,CD105+,CD34-,CD36-,CD45- **RT-PCR**: OCT4+,NANOG+,SOX2+	Adipogenic, osteogenic	(Singh et al. 2013)
	AP+ **ICC**: Oct4+,Nanog+,Sox2+,CD73+,CD90+,CD105+,CD34- **RT-PCR**: CD73+,CD90+,CD105+ **qPCR**: OCT4+,NANOG+,SOX2+	Adipogenic, chondrogenic, osteogenic	(Sreekumar et al. 2014)

697 + : positive; - : negative; ± : weakly positive; ICC: immunocytochemistry

698 **Table 5**. Clinical applications of foetal MSCs in domestic animals.

MSCs source	Species	Clinical application	Ref.
AM	Sheep	Diskectomy with bone graft	(Goldschlaget et al. 2011)
	Horse	**Spontaneous** tendon and ligament injuries	(Lange-Consiglio et al. 2012; 2013b; 2013c)
	Pig	Myocardial ischemia	(Kimura et al. 2012)
AF	Sheep	Diaphragmatic repair with graft	(Fuchs et al. 2004; Turner et al. 2011)
		Prenatal tracheal reconstruction with scaffold	(Kunisaki et al. 2006b; Gray et al. 2012)
		Diaphragmatic repair	(Kunisaki et al. 2006c)
		Prenatal treatment with lentiviral transducted cells	(Shaw et al. 2011)
		Prenatal cell-based heart valves implantation	(Weber et al. 2012)
		Tendon injuries with nucleofected cells	(Colosimo et al. 2013a)
	Swine	Cardiac ischemia	(Sartore et al. 2005)
		Myocardial infarction in mouse	(Peng et al. 2014)
	Horse	**Spontaneous** decubitus ulcers with PRP	(Iacono et al. 2012c)
UCB	Horse	Intra-articular injection	(Carrade et al. 2011)
		Spontaneous tendinitis of superficial digital flexor tendon	(Kang et al. 2013)
		Spontaneous tendon and ligament disorders	(Van Loon et al. 2014)

	Dog	Spinal cord injury	(Lim et al. 2007; Park et al. 2011)
		Diaphyseal defect in the radius	(Jang et al. 2008)
		Bone regeneration in ectopic implantations	(Byeon et al. 2010)
		Segmental bone defects	(Kang et al. 2012)
WJ/UCM	Swine	Transplantation into rat brains	(Weiss et al. 2003)
		Allogeneic engraftment in the neonatal intestine	(Miller et al. 2012)
	Caprine	Skin wounds	(Azari et al. 2011)
		Skin wounds in rat	(Pratheesh et al. 2014)
	Horse	Intra-articular injection	(Carrade et al. 2011)
	Dog	Segmental bone defects	(Kang et al. 2012)
		Spinal cord injuries	(Ryu et al. 2012)

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