Sex differences in umbilical cord

Subjects: Others

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Biological differences between sexes should be considered in all stages of research, but there is still a lack of stratification by sex despite primary cultured cells retain memory of the sex and of the donor. The sex of donors in biological research must be known because variations in cells and cellular components can be used as end points, biomarkers and/or targets of pharmacological studies. This selective review focuses on the current findings regarding sex differences observed in the umbilical cord, a widely used source of research samples, both in the blood and in the circulating cells, as well as in the different cellular models obtainable from it. Moreover, an overview on sex differences in fetal programming is reported. As it emerges that the sex variable is still often forgotten in experimental models, we suggest that should be mandatory to adopt a sex oriented research, because only awareness of these issues can lead to innovative research.

Keywords: umbilical cord ; Sex differences ; preclinical research

Sex differences in umbilical cord

Human umbilical cord has no particular ethical impediments, is non-tumorigenic, and less immunogenic, representing an advantageous experimental source over other cell sources [1][2]. Moreover, it is a good experimental model for studying and understanding sex differences that characterize cardiovascular system [3]. The umbilical artery is made up of two main layers: an outer layer of muscle cells is found in a circular fashion and an inner layer with more irregularly available cells. Moreover, the umbilical cord contains Wharton's Jelly (WJ), a gelatinous substance made largely from mucopolysaccharides, which protects the blood vessels inside. WJ is enveloped in amniotic epithelium or, at the fetal end, a Malpighian keratinized epithelium, and it is a tissue that is active metabolically, involved in fluid exchange between umbilical vessels and amniotic fluid [4].

Sex-specific differences in fetus growth appear early in the pregnancy and have long been recognized [5]. Cell divisions is more rapid in male embryos than in female ones [6], and male fetuses growth seems to be greater than the female ones. Sex differences in the placenta are also described: globally males have larger and heavier placenta, and birth weight/placental weight ratio than females [7][8][9]. in addition, fetal sex may affect the outcome of pregnancies: male sex is a risk factor for adverse pregnancy outcome, including preterm birth, premature rupture of membranes, gestational diabetes and macrosomia, motor and cognitive outcomes, and a lower likelihood of survival in intensive care [7][10].

Several sex differences are reported in cord blood cells, plasma and serum (Table). As regard cellular models, some sex differences exist in HUVECs. In fact a higher rate of proliferation and migration, and higher levels of both the gene and protein for nitric oxide synthase 3 are observed in female cells than in male ones [11]. By contrast male HUVECs seems to have a higher degree of constitutive autophagy. Moreover, HUVECs from males resulted more apoptotic than female ones after serum starvation, while no significant sex differences were observed in the percentage of necrotic cells [12]. 70 genes are differentially expressed between the sexes: female HUVECs have a larger levels of genes related to the immune response and some genes involved in metabolism (for example, leptin, insulin receptors and some apolipoproteins), and that they also have a greater capacity to form tubes and tolerate the stress of serum deprivation better than their male counterparts [13].

As regards HUAECs no sex-related differences have been reported at present and to our knowledge, probably because they are a less used source of endothelial cells. few results are available for HUASMCs: constitutive autophagy is similar between male and female HUASMCs, but they differently respond to pharmacological stimulations: serum starvation and rapamycin treatment (immunosuppressant and anticancer agent acting as a selective inhibitor of mTOR protein kinase, a pleiotropic agent in nutrient detection and signaling) [14] promote authophagy in both sexes, but especially in females cells increasing LC3II/I ratio and decreasing the phosphorylation of the autophagic regulator mTOR.

Significant higher gene expression of octamer-binding transcription factor 4 (OCT4), pluripotency gene, and the DNA-methyltransferase epigenetic modulator gene (DNMT1) was observed in male WJ-MSCs than in female ones, while no sex differences has been detected in the expression levels of other stemness regulating genes as SOX2, NANOG, and C-MYC [15]. Sex mayalso affect the potential and efficiency of WJ-MSCs differentiation and autophagy: no significant differences between males and females were observed for miR-145-5p (target: OCT4 gene), and miR-185-3p (target: DNMT1 gene), while miR-148a-3p (target: OCT4 gene) was significantly lower in males. In addition, the autophagic marker LC3II/I ratio was higher in female cells than in male ones, indicating a higher constitutive autophagy in female cells [16]. Another study showed that baculoviral IAP repeat-containing protein 2 (BIRC2) and BIRC3 genes, which inhibit apoptosis by interfering with the activation of caspases, are higher, although not significantly, in WJ stem cells from male newborns, indicating, perhaps a sex difference in the sensitivity to apoptosis [17].

From this overview, it emerges that the sex variable is still often forgotten in experimental models. In fact, for some cell types, which may be important for understanding sex differences in the pathophysiology of the cardiovascular system, such as the one we have analyzed, there is no data. The knowledge of sex differences is fundamental to the improvement of therapeutic response at least for cardiovascular diseases in both men and women, as they are the main cause of mortality and morbidity for both sexes.

Table 1. Sex differences in cord blood, plasma and serum

Parameters	Source	M vs F	Comments	Ref
Total and free testosterone	serum (venous)	> M	Dehydroepiandrosterone sulfate from arterial serum > than that from vein only in F	[18]
Estradiol	serum (venous)	> M		[18]
Inhibin	serum (venous)	> M		[18]
Cortisol and corticosterone	serum (arterial and venous)	> F		[19][20]
GH	serum (venous)	> M		[21]
Leptin	serum (arterial and venous)	> F		[22]
Insulin and C-peptide	plasma	> F		[23][24]
15-F(2t)-isoprostane	plasma	> M	Premature twins	[25]
Gluthatione	umbilical cord vein	> M	Segments of umbilical cord vein perfused with tert-butylhydroperoxide	[26]
Mononuclear cell mitochondrial DNA copies	cord blood	> F	After prenatal exposure to carbon monoxide as air pollutant	[27]
DNA methylation	cord blood	> F	Number of methylated CpGs sites	[28]
Red blood cells	cord blood	> M		[29][30]
Hematocrit	cord blood	> M		[29][30]

Hemoglobin	cord blood	> M		[29][30]
Mean corpuscular hemoglobin concentration	cord blood	> M		[29][30]
Mean corpuscular volume	cord blood	> F		[29][30]
Platelet	cord blood	> F		[29][30]
White blood cells	cord blood	> F	Lymphocyte, monocyte, eosinophil, basophil > M , neutrophil, metamyelocyte, myelocyte, and promyelocyte ratios > F	[30]
CD34+ progenitor cells	cord blood	> M	M have higher capacity to produce colonies	[31][32]
ILC2s	cord blood	> M		[33]
CD34+KDR+ progenitor cells	cord blood	> F		[34]

M = males; F = females

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