Encore – Sex Dependency of the Proteome

Medicine has for a long time assumed that non-reproductive organs and tissues in the human body are independent of sex / gender, basing all their studies on the standard of a – mostly young – healthy male. It took centuries till this attitude has changed and the term "gender medicine" and its background were generally accepted. For instance, only in 2010 the first gender medicine unit of Austria was established, at the Medical University of Vienna (https://www.meduniwien.ac.at/hp/gender-medicine/). Also animal models for pharmacology have often been based on males, mainly rodents, to avoid influence of female hormonal cycles.

Having accepted sex-dependent differences in the chromosomes, the genes and physiology, also as a function of age, it has become clear that this diversity has also to be reflected in the protein setup, as proteins are the molecules responsible for many of the actions in the body. Here comes proteomics into play. In a previous issue (https://www.sciencedirect.com/journal/journal-of-proteomics/vol/178/suppl/C) we have collected papers that showed the usefulness of proteomics to investigate sex differences. Topics in that issue span from impact of sex-specific protein patterns and their changes in human diseases (cardiovascular diseases [1], cognitive disorders or Alzheimer's disease [2]) to susceptibility to toxins (mycotoxins [3]). Gender-dependent differences are similarly detectable in animals [e.g. pig, saliva [4]), whereof some serve as models of disease [5, 6]. Influence of animal sex on susceptibility in toxicological experiments and its reflection in the proteome have already been reported previously (in aquatic animals [7] or mice [8, 9]). Besides these male-female comparisons of non-reproductive tissues/organs [10], some contributions dealt with the study of reproductive organs [11] or physiological changes during pregnancy and lactation [12, 13]. Last, but not least, sex-specific differences were also shown for plants, having an influence in cases of soil with low nutritional value [14].

Given the importance of this area of research, and to investigate the potential impact on additional, not yet covered topics, we collected in the present, smaller issue additional examples. In the field of human medicine, investigation on HUVECs from twin pairs of opposite sex excludes factors like life-style or environment often influencing other studies [15]. Specific enamel proteins allow sex-determination even in 5000-year-old human teeth [16]. The hippocampus proteome of male and females piglets is not affected in the same way during intra-uterine growth restriction [17]. Also the proteome of meat (beef, pork) reflects sex of the animals, besides influence of breed, rearing conditions and diet [18, 19]. Similarly, muscular, hepatic and adipose tissues proteomes of muskox, a ruminant living in the arctic tundra of Northern America, show sex-dependent differences [20]. A last example compares proteomes of reproductive tissues at different developmental stages of the tobacco cutworm, whose larvae are well-known for damaging agricultural crops [21].

The few examples given here show two things: for one, today's proteomic methods are sensitive enough to determine minor differences in protein patterns (both qualitative and quantitative aspects), and, second, sex/gender may influence this pattern. However, some other factors, e.g. in animals: breed, diet and developmental age for animals, have also an impact, sometimes an even more marked one [19]. It needs careful testing to assess which factors prevail or to find (sex-, breed- etc.) independent factors if looking for "biomarkers" [18].

For further reading: The importance of gender studies has been acknowledged by the European Commission in a Report of the Expert Group "Innovation through Gender" [22], compiling projects in different fields.

References:

1) Baetta R, Pontremoli M, Fernandez AM, Spickett CM, Banfi C.
Proteomics in cardiovascular diseases: Unveiling sex and gender differences in the era of precision medicine.
J Proteomics. 2018 Apr 30;178:57-72. doi: 10.1016/j.jprot.2018.03.017. Epub 2018 Apr 3.

2) Reumiller CM, Schmidt GJ, Dhrami I, Umlauf E, Rappold E, Zellner M.
Gender-related increase of tropomyosin-1 abundance in platelets of Alzheimer's disease and mild cognitive impairment patients.
J Proteomics. 2018 Apr 30;178:73-81. doi: 10.1016/j.jprot.2017.12.018. Epub 2017 Dec 24.

3) Soler L, Oswald IP.
The importance of accounting for sex in the search of proteomic signatures of mycotoxin exposure.
J Proteomics. 2018 Apr 30;178:114-122. doi: 0.1016/j.jprot.2017.12.017. Epub 2017 Dec 27.

4) Gutiérrez AM, Montes A, Gutiérrez-Panizo C, Fuentes P, De La Cruz-Sánchez E.
Gender influence on the salivary protein profile of finishing pigs.
J Proteomics. 2018 Apr 30;178:107-113. doi: 0.1016/j.jprot.2017.11.023. Epub 2017 Dec 1.

5) Theuring F, Neumann B, Scheler C, Jungblut PR, Schwab K.
Sex differences in murine myocardium are not exclusively regulated by gonadal hormones.
J Proteomics. 2018 Apr 30;178:43-56. doi: 10.1016/j.jprot.2017.12.005. Epub 2017 Dec 19.

6) Audano M, Maldini M, De Fabiani E, Mitro N, Caruso D.
Gender-related metabolomics and lipidomics: From experimental animal models to clinical evidence.
J Proteomics. 2018 Apr 30;178:82-91. doi: 10.1016/j.jprot.2017.11.001. Epub 2017 Nov 6.

7) Liang X, Feswick A, Simmons D, Martyniuk CJ.
Environmental toxicology and omics: A question of sex.
J Proteomics. 2018 Feb 10;172:152-164. doi: 0.1016/j.jprot.2017.09.010. Epub 2017 Oct 14.

8) Miller I, Serchi T, Cambier S, Diepenbroek C, Renaut J, Van den Berg JHJ, Kwadijk C, Gutleb AC, Rijntjes E, Murk AJ.
Hexabromocyclododecane (HBCD) induced changes in the liver proteome of eu- and hypothyroid female rats
Toxicol Lett. 2016 Mar 14;245:40-51. doi: 10.1016/j.toxlet.2016.01.002. Epub 2016 Jan 12.

9) Miller I, Diepenbroek C, Rijntjes E, Renaut J, Teerds KJ, Kwadijk C, Cambier S, Murk AJ, Gutleb AC, Serchi T.
Gender specific differences in the liver proteome of rats exposed to short term and low-concentration hexabromocyclododecane (HBCD)
Toxicol Res (Camb). 2016 Jun 30;5(5):1273-1283. doi: 10.1039/c6tx00166a. eCollection 2016 Sep 1.

10) Gianazza E, Miller I, Guerrini U, Palazzolo L, Parravicini C, Eberini I.
Gender proteomics I. Which proteins in non-sexual organs.
J Proteomics. 2018 Apr 30;178:7-17. doi: 10.1016/j.jprot.2017.10.002. Epub 2017 Oct 6.

11) Gianazza E, Miller I, Guerrini U, Palazzolo L, Parravicini C, Eberini I.
Gender proteomics II. Which proteins in sexual organs.
J Proteomics. 2018 Apr 30;178:18-30. doi: 10.1016/j.jprot.2017.10.001. Epub 2017 Oct 6.

12) D'Silva AM, Hyett JA, Coorssen JR.
Proteomic analysis of first trimester maternal serum to identify candidate biomarkers potentially predictive of spontaneous preterm birth.
J Proteomics. 2018 Apr 30;178:31-42. doi: 10.1016/j.jprot.2018.02.002. Epub 2018 Feb 13.

13) Ceciliani F, Lecchi C, Urh C, Sauerwein H.

Proteomics and metabolomics characterizing the pathophysiology of adaptive reactions to the metabolic challenges during the transition from late pregnancy to early lactation in dairy cows.
J Proteomics. 2018 Apr 30;178:92-106. doi: 10.1016/j.jprot.2017.10.010. Epub 2017 Oct 18.

14) Song H, Lei Y, Zhang S.
Differences in resistance to nitrogen and phosphorus deficiencies explain male-biased populations of poplar in nutrient-deficient habitats.
J Proteomics. 2018 Apr 30;178:123-127. doi: 0.1016/j.jprot.2017.11.013. Epub 2017 Nov 21.

15) Witt E, Lorenz M, Völker U, Stangl K, Hammer E, Stangl V.
Sex-specific differences in the intracellular proteome of human endothelial cells from dizygotic twins.
J Proteomics. 2019 Apr 2;201:48-56. doi: 10.1016/j.jprot.2019.03.016. [Epub ahead of print]
JPROT-D-18-00677

16) Froment C, Hourset M, Sáenz-Oyhéréguy N, Mouton-Barbosa E, Willmann C, Zanolli C, Esclassan R, Donat R, Thèves C, Burlet-Schiltz O, Mollereau C.
Analysis of 5000 year-old human teeth using optimized large-scale and targeted proteomics approaches for phenotypic assessment
JPROT-D-19-00043

17) Valent D, Yeste N, Hernández-Castellano LE, Arroyo L, García-Contreras C, Vázquez-Gómez M, González-Bulnes A, Bendixen E, Bassols A.
SWATH-MS quantitative proteomic investigation of intrauterine 1 growth restriction in a porcine model reveals sex differences in hippocampus development
J Proteomics. 2019 Jul 30;204:103391. doi: 10.1016/j.jprot.2019.103391. Epub 2019 May 24
JPROT-D-19-00018

18) Picard B, Gagaoua M, Al Jammas M, Bonnet M.
Beef tenderness and intramuscular fat proteomic biomarkers: Effect of gender and rearing practices.
J Proteomics. 2019 May 30;200:1-10. doi: 10.1016/j.jprot.2019.03.010. Epub 2019 Mar 17.
JPROT-D-19-00072

19) Paredi G, Mori F, de Marino MG, Raboni S, Pietro D, Fiego L, Mozzarelli A.
Is the protein profile of pig *Longissimus dorsi* affected by gender and diet?
J Proteomics. 2019 Aug 30;206:103437. doi: 10.1016/j.jprot.2019.103437. Epub 2019 Jul 2.

JPROT-D-19-00177

20) Ribeiro DM, Planchon S, Leclercq CC, Raundrup K, Alves SP, Bessa RJB, Renaut J, Almeida AM. The muscular, hepatic and adipose tissues proteomes in muskox(Ovibos moschatus): Differences between males and females
J Proteomics. 2019 Sep 30;208:103480. doi: 10.1016/j.jprot.2019.103480. Epub 2019 Aug 5.
JPROT-D-19-00268

21) Sun R, Sun Z, Chen Y, Zhu F, Li Y, Zhong G, Yi X. Comparative proteomic analysis of sex determination-related proteins in ovary and testis at different stages of *Spodoptera litura*
J Proteomics. 2019 Aug 30;206:103439. doi: 10.1016/j.jprot.2019.103439. Epub 2019 Jul 2.
JPROT-D-19-00152

22) European Commission. Gendered Innovations. How Gender Analysis Contribute to Research. Directorate Generla for Research & Innovation. EUR 25838, 2013.
ISBN 978-92-79-25982-1 doi:10.2777/11868.

158 Graphical Abstract

159

160

161

162

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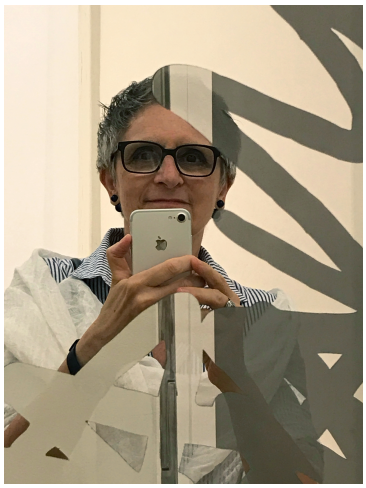

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