

Sex omission and male bias are still widespread in cell experiments

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ABSTRACT

Summary & Relevance Sex is an important biological variable, but it has not received sufficient attention in basic and preclinical studies. Recently, international funding agencies and renowned journals are trying to integrate sex as a variable in every research steps. **Aims & Objectives** We wanted to see whether researchers' perception for cell sex has improved as a result. We examined the sex notation of the cells in all the articles published in American Journal of Physiology-Cell Physiology in 2018. **Method** Sex notation was also analyzed by cell species and type and source in the article. **Results** Of the 107 articles reporting cell experiments, 50 articles (47%) reported sex of the cells, while 57 articles (53%) did not. Among the 50 articles with sex description, 17 articles (34%) used both male and female cells in the study, while 23 articles (46%) used male cells only and 10 articles (20%) used female cells only. We found that almost all researchers were indifferent to the sex of the cell lines they used. The sex information of some commercially available cell lines was readily available in web sites, but the researchers rarely described it. Meanwhile, 64% of articles showing data from primary cells reported the sex of the cells. Sex omission was more frequent for human primary cells than for non-human primary cells. Researchers reported sex of the primary cells more faithfully when they isolated the cells by themselves than when they purchased the cells. In articles describing experiments using rodent primary cells, only about 15% used both male and female cells. Whereas over half of the studies showing data from either mouse or rat primary cells used only male cells revealing evident male bias. **Conclusions** Our survey show that sex omission and male bias is still prevailing in cell experiments. Integrating sex as an important biological variable is imperative to enhance the accuracy and reproducibility of cell-based studies which provide basic information for subsequent preclinical and clinical study design. Our research showing male bias in cellular experiments is related to UN sustainable development goal 5 'Gender Equality'.

Introduction

Sex bias in cell experiments in basic research stages may hinder relating the obtained results to animal studies and human applications. Many studies have demonstrated that the sex of cells can affect their differentiation, proliferation, stress responses, and apoptosis. However, there continues to be a lack of interest in the sex of cells used in basic research. Sex omission and sex bias are easily observable in publications reporting cell experiments. When 618 articles published in several journals from 2011 to 2012 were examined, 76% of the articles did not describe the sex of the cells they had studied. Of the papers that did specify the sex, 71% used only male-originating cells, 21% used only female-originating cells, and 7% used cells from both sexes. However, just seven (1%) of the 618 articles showing data from both male and female animals carried out sex-based analysis for the obtained results. Shah et al. examined the sex of the cell lines used in 100 randomly selected articles published in the American Journal of Physiology-Cell Physiology (AJP-CP) in 2013. They found that 75% of the articles assessed did not describe the sex of the cells, 20% used male cells only, and 5% used female cells only, while no study had incorporated both male and female cells into its design. To remedy this situation, the NIH, the European Commission, and the Canadian Institutes of Health Research (CIHR) require that researchers integrate sex as a biological variable in biomedical research steps from hypothesis to publication. World-renowned international journals have also pushed to implement the consideration of sex in research to help increase the reproducibility and transparency of the published data. To discern whether researchers' perceptions regarding cell sex have been improved with these efforts, we repeated the survey of Shah et al. by examining the sex notations and ratio of the cells used in all the articles published in AJP-CP in 2018.

Methods

To determine how the sex of the cells has been described in articles, we examined the papers published in AJP-CP in 2018. Using the PubMed query terms "Am J Physiol Cell Physiol" [jour] AND ("2018/01/01" [PPDat]: "2018/12/31" [PPDat]) yielded a total of 149 articles. Two researchers independently reviewed the 149 PubMed search hits and compared the results. Whenever discordance arose between the two researchers, they reviewed the papers together and reached a consensus. 107 articles were original articles that presented cell experimental data, and the remaining 42 were articles that did not present cell experimental data. Each of the 107 papers was examined regarding whether the sex of the cells used was reported or not. The papers were also assessed to determine whether the sex notations and ratio were influenced by species, type, and source of the cells. Sex-specific organ-derived cells such as endometrial cells or oocytes were regarded as having their sex indicated even though there was no direct sex description provided for the cells. All of the other cells were regarded as having their sex defined only if they were accompanied by a direct sex description.

Discussion

We found that almost all researchers were indifferent toward the sex of the cell lines they used. Meanwhile, 64% of articles showing data from primary cells reported the sex of the cells. Sex omission was more frequent for human primary cells than for nonhuman primary cells. Researchers reported the sex of primary cells more faithfully when they isolated the cells by themselves (75%) than when they purchased the cells (25%). In articles describing experiments performed using rodent primary cells, more half of studies used only male cells, revealing evident male bias. Our survey suggests that sex omission and male bias is still prevalent in cell experiments. Integrating sex as an important biological variable is imperative to enhance the accuracy and reproducibility of cell-based studies, which provide basic information for subsequent preclinical and clinical study designs. Our research showing male bias in cellular experiments is related to UN sustainable development goal 5 'Gender Equality'.

Results

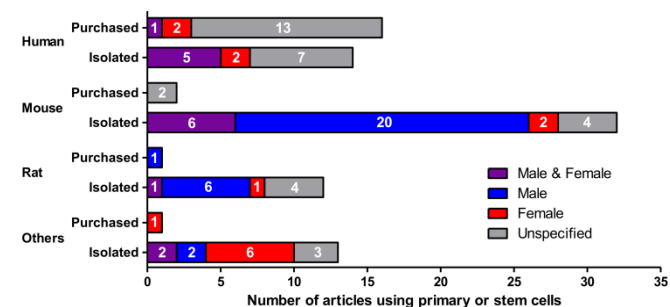


Figure 3. Distribution of the included articles by sex depending on cell type and species. The articles describing the sex of the cells used were divided according to the cell type(s) and species mentioned. When multiple species or types of cells were used in one article, that specific article was counted as one entry in each of the appropriate categories.

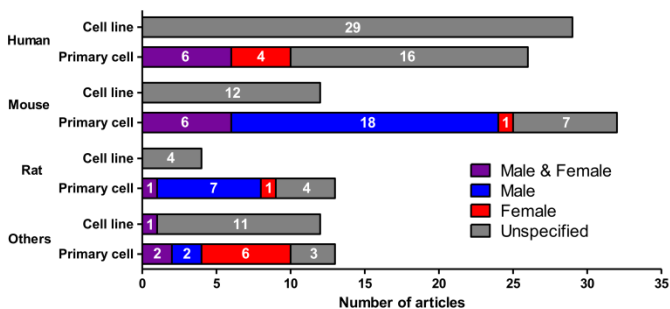


Figure 4. Distribution of articles according to the sex of primary cells depending on whether they were purchased or personally isolated. The number of articles describing the sex of the cells was indicated according to how the researchers obtained the cells from each species. When cells from multiple species and/or sources were used in one study, that specific article was counted as one each in the different appropriate categories.

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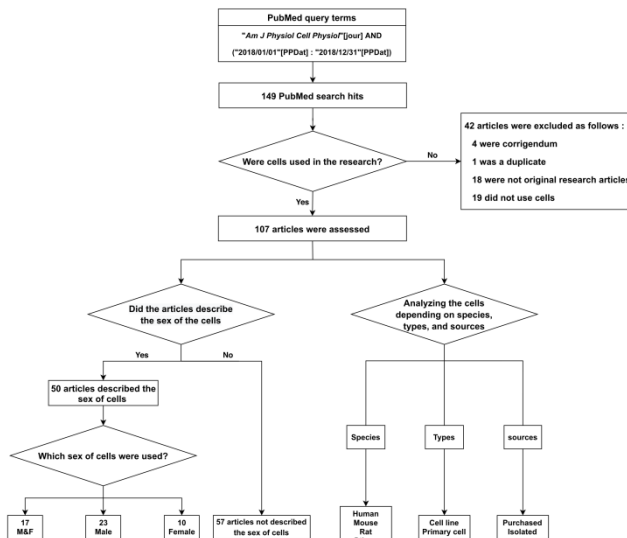


Figure 1. Flowchart for analyzing sex notations and ratio in the articles reporting on the conduct of cell experiments.

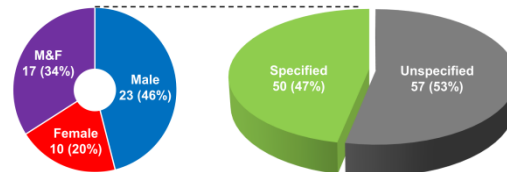


Figure 2. Distribution by sex of articles published in AJP-CP in 2018. Original research articles (n = 107) describing experiments using cells were analyzed. The number and percentage of articles describing the sex of the cells they used in the studies are presented.