


Response

To the Editor:

I thank Dr Spanbroek and colleagues for their comments on our recent article in *CHEST.* We chose two cohorts for the study because we had the opportunity to do so and could not predict the results. In fact, as pointed out, the cohorts were quite different in composition in terms of sex predominance and age variations and showed results, consistent in both cohorts, of significant increases in plasma levels of desmosine and isodesmosine (D/I) in subjects exposed to secondhand smoke. We are not aware of data showing differences between men and women in levels of D/I in normal subjects. There may be a relation between aging and increases in D/I in plasma in normal subjects, but we have not observed such a correlation in the current data available to us or in currently published studies. Larger series of studies of normal subjects of various ages may show such a relation to age, which has been suggested in aging rats.

None of the secondhand smoke-exposed subjects were former smokers. The active smokers in both cohorts were free of respiratory symptoms and were considered to be in normal health. The measurements of D/I in the subjects exposed to secondhand smoke were not only an average of two analyses but were based on recoveries of known amounts of spiked samples of plasma. This greatly improved accuracy and repeatability. Subsequent analyses using the pyridoline standard showed acceptable similarities when compared with our previously published measurements.

A stable deuterium isotope, which is not yet available, is the ideal internal standard. We are in the process of synthesizing this standard (Yamada et al, unpublished data, November 2011). The deuterium used in the reference cited by the respondents was made by ion exchange reaction, which is not stable during hydrolysis. As pointed out, I agree that D/I remain an interesting marker for the evaluation of elastin breakdown and have so stated in a recent publication.

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Risk of Teratoma Formation After Transplantation of Induced Pluripotent Stem Cells

To the Editor:

I read with great interest the article by Yang et al in a recent issue of *CHEST* (November 2011), which clearly demonstrates that IV administration of induced pluripotent stem (iPS) cells reduces endotoxin-induced acute lung injury in mice. Regarding the possibility of teratoma formation after transplantation of iPS cells, I have several concerns from the viewpoint of human clinical application in the future.

First, it would be interesting to know the reason why there would be no teratoma formation in the present study. Recently, it has been revealed that mouse iPS cell-derived cells have immunogenicity and can be rejected immunologically, even when transplanted into syngenic mice, because several genes are found to be overexpressed in teratomas, which will induce immune responses. On the other hand, it has been shown that embryonic stem (ES) cell-derived cells have no immunogenicity and can be engrafted as teratomas. In the present study, it is not clear whether the lack of teratoma formation is attributable to the types of cells the authors used or the method they used to inject cells. Control experiments, either by using ES cells or by direct intratracheal injection, would clarify this point.

Second, it would be safer to inject differentiated cells rather than undifferentiated iPS cells in order to avoid potential teratoma formation. Recently, there has been a commentary by Okita et al against the article describing immunogenicity of iPS cells. The commentary mentioned that, for human medical applications, iPS-derived cells (ie, differentiated cells), but not iPS cells themselves (ie, undifferentiated cells), would be injected into patients. Based on this philosophy, there would be no efficacy, even when differentiated cells from iPS cells would be administered into mice with endotoxin-induced acute lung injury.

Finally, as mentioned by the authors, because autologous iPS cells would be hardly available for patients with acute lung injury, allogeneic iPS or ES cells should be applied. How about allogeneic transplantation in mice? The use of immunosuppressants for allotransplantation would be prohibited because...
of the risk of endotoxin-induced acute lung injury. If acute rejection within 24 or 48 h is not found to be a serious problem for efficacy, allotransplantation without immunosuppressants would be suitable for endotoxin-induced acute lung injury.

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Response

To the Editor:

We thank Dr Masuda for his interest in our recent article in CHEST. Dr Masuda expressed relevant opinions on the potential mechanism of teratoma formation after transplantation of induced pluripotent stem (iPS) cells.

In a recent study, Zhao et al examined the immunogenicity of iPS cells between embryonic stem (ES) cells isolated from inbred C57BL/6 (B6) mice and allogeneic ES cells from 129/SvJ mice. Whereas injection of ES cells from B6 mice induced teratoma formation, allogeneic ES cells derived from 129/SvJ were unable to form teratomas due to immune rejection by the recipients. A subsequent experiment was performed to evaluate teratoma formation in reprogrammed iPS cells from B6 mice by either the retroviral approach (ViPS cells) or a novel episomal approach (EiPS cells). In contrast to teratoma formation in ES cells from B6 mice, teratomas were immune rejected in reprogrammed iPS cells by B6 recipients in both the ViPS cell and EiPS cell methods. A T-cell-dependent immune response was shown in the teratomas that resulted in tissue damage and teratoma regression. Although teratoma formation was demonstrated by both methods, the ViPS cells method appeared to be superior at eliciting a greater immune response than the EiPS cells method. In addition, the inflammatory microenvironment and circulatory immune system may facilitate the engraftment of transplanted iPS cells but prevent teratoma formation.

Moreover, to decrease the potential of teratoma formation in iPS cell-based therapy, a recent commentary by Okita et al examined the use of iPS cell-derived differentiated cells instead of undifferentiated iPS cells for transplantation in medical applications. Differentiated cells, such as ES cell-derived alveolar epithelial type 2 cells, have shown a therapeutic effect in mice with acute lung injury (ALI). However, the immunogenicity of iPS cell-derived differentiated cells in autogenic or allogenic transplantation is still unclear. Therefore, further studies are warranted to explore the immune response among transplanted iPS cell-differentiated cells, inflammatory cells, and host cells in ALI.

Dr Masuda mentioned the therapeutic potential of allotransplantation with or without immunosuppressants for endotoxin-induced ALI. Interestingly, immunosuppressants may enhance the differentiation of iPS cells. Fujisawa et al have reported that cyclosporine drastically increases cardiomyocyte induction from human iPS cells, and these cells showed various cardiac marker expressions and ultrastructural features of cardiomyocytes.

In conclusion, we agree that autologous iPS cell therapy currently offers many technical challenges for the treatment of patients with ALI. However, a better understanding of the reprogramming of iPS cells, graft rejection, and teratoma formation may improve the potential of this technology for the treatment of patients with ALI.

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