To Editor, World Journal of Stem Cells

We appreciate your kindly giving us an opportunity to submit a revised version of our manuscript (NO.: 22166.). We are submitting our responses to the reviewers' comments. Thanks to the valuable comments from the reviewers, we believe that our manuscript has been up-graded.

Comments of Reviewer 503118

The manuscript titled, " Human pluripotent stem cells: towards therapeutic development for the treatment of lifestyle diseases" by Nishio et. al. discusses application of iPS cells for lifestyle diseases. While overall the manuscript is well written, a careful editing is needed to correct minor mistakes, for example on page 6, paragraph 2, line 6, "commercially available sauces....." should read as "commercially available sources.....". With these corrections incorporated, reviewer recommends accepting the manuscript for publication.

Classification: B
Language evaluation: B
Conclusion: Accept

Our response:
Thanks to the reviewer's kind comment, we could re-check our previous manuscript. In our revised manuscript, we have corrected the errors.

Comments of Reviewer 2446098

In general, this is an interesting review paper. Authors should focus more on the topic: human pluripotent stem cells. Either hESC or hiPSC should be further discussed, e.g. other than endothelial differentiation, cardiomyocyte, neuron should be covered/involved in.

Classification: C

Language evaluation: A
Conclusion: High priority for publication

Our response:
We respect the reviewer's comment and tried to expand the topic of our review by adding descriptions regarding hESC/hiPSC-derived cardiomyocytes and neurons toward the therapeutic development of lifestyle diseases. However, after a process of try and error for more than a week, we have concluded that an expansion of the topic rather deteriorates the balance and quality of our review. We apologize that we could not respond to the reviewer's request. Nevertheless, we believe that our review will stimulate and inspire the mind of the readers.

Additional notes.
As we described in the cover letter of our initial submission, we originally drew the illustrations in Figure 2 by referring the figure 9-2 in the Japanese version of Langman's medical embryology, 8th ed (reference #35). Although we do not think that our Figure 2 infringes copyright, we sent an e-mail of inquiry to the publisher (Wolters Kluwer Company) to make assurance double sure on Sep 4th. Until now, we have not received any responses. I suppose that they do not think our Figure 2 infringes copyright, either. In our revised manuscript, we additionally referred a paper by Atit et al (reference #36), which reported a similar finding about the location of brown adipocyte progenitors. We believe that this additional reference not only strengthens the scientific validity of Figure 2 but also guarantees appropriateness from a legal standpoint.

Below is the copy of the figure 9-2 in the Japanese version of Langman's medical embryology, 8th ed (reference #35).

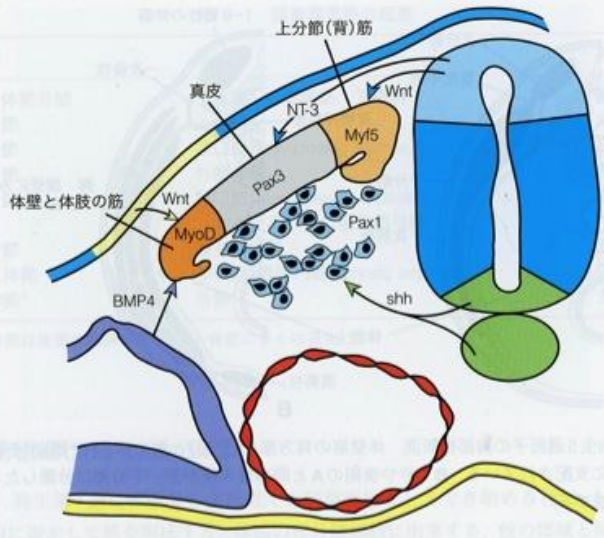

図9-2 体節の分化を制御する遺伝子の発現パターン
ソニック・ヘッジホッグ(*shh*)が脊索と神経管の底板から分泌され，これが体節の腹側部に作用して椎板を作る．椎板では*PAX1*が発現し，続いてこれが軟骨化と椎骨形成を制御する．神経管の背側部から分泌されるWnt蛋白は*PAX3*を活性化し，これが皮筋板の境界を定める．またWnt蛋白は体節の背内側部に作用して上分節筋(背筋)を形成させ，筋特異性遺伝子*Myf5*を発現させる．体節の背側中央部は神経管背側部に発現するニューロトロフィン3(*NT-3*)によって真皮への分化を方向づけられる．下分節(体肢と体壁)筋は，活性化作用をもつWnt蛋白と抑制作用をもつBMP4蛋白の共同作用により体節の背外側部より作られる．Wnt蛋白とBMP4蛋白は共同して*MyoD*の発現を活性化する．

の結合組織は神経堤の細胞に由来し，頸部と後頭域では体節中胚葉から生じ，体壁と四肢では壁側中胚葉に起源する．

■筋前駆細胞に由来する構造

第5週の終わりまでに，のちに筋に分化する細胞は2つの部分に集まる．背側の小部分すなわち**上分節**(epimere)は，筋節に再構成される体節の背内側の細胞から作られ，より大きな腹側の部分すなわち**下分節**(hypomere)は，体節の背外側の細胞の遊走によって形成される(図9-1B)．分節的筋を支配する神経も上分節へ分布する**一次後枝**(dorsal primary ramus)と，下分節に分布する**一次前枝**(ventral primary ramus)とに分かれる(図9-3B)．これらの神経は，はじめに分布した筋の部分が遊走する間もその筋に付いたままである．

上分節の筋は脊柱の**伸筋**群を形成し，一方，下分節の筋は体肢と体壁の筋を作る(図9-3B)．