Claims

1. A method of producing a human cell aggregate comprising an adenohypophysis or a precursor tissue thereof, comprising:

(1) rapidly aggregating dispersed human pluripotent stem cells to form one aggregate in one culture compartment and culturing the aggregate of human pluripotent stem cells in suspension in a serum-free medium containing an exogenous bone morphogenetic protein signal transduction pathway activating substance and a substance activating or enhancing the Shh signal pathway to obtain a human cell aggregate comprising a hypothalamus neuroepithelial tissue and a surface ectoderm, and

(2) further culturing the obtained human cell aggregate comprising the hypothalamus neuroepithelial tissue and the surface ectoderm in suspension in a serum-free medium containing an exogenous bone morphogenetic protein signal transduction pathway activating substance and a substance activating or enhancing the Shh signal pathway to induce formation of hypophysial placode and/or Rathke's pouch in the surface ectoderm, thereby obtaining a human cell aggregate comprising i) hypothalamus neuroepithelial tissue, and ii) hypophysial placode and/or Rathke's pouch ,

in step (2) the concentration of the bone morphogenetic protein signal transduction pathway activating substance being decreased to half every 2 - 4 days or being reduced to not more than 1/4 compared to that at the start of step (2),

wherein the concentration of the bone morphogenetic protein signal transduction pathway activating substance is decreased or reduced by medium exchanges;

wherein the adenohypophysis is a tissue containing at least one kind of anterior or intermediate pituitary hormone-producing cell ,

and wherein the bone morphogenetic protein signal transduction pathway activating substance is selected from the group consisting of BMP2, BMP4, BMP7 and GDF5,

and wherein the substance activating or enhancing the Shh signal pathway is selected from the group consisting of proteins belonging to the Hedgehog family, Shh, Shh receptor, Shh receptor agonist, Purmorphamine and Smoothened Agonist (SAG)(3-Chloro-N-[trans-4-(methylamino)cyclohexyl]-N-[[3-(4-pyridinyl)phenyl]methyl]- benzo[b]thiophene-2-carboxamide.

2. The production method according to claim 1, wherein the medium used in step (2) further comprises FGF2.

3. The production method according to claim 1 or 2, wherein step (2) is performed for not less than 6 days.

4. The production method according to any one of claims 1 to 3, which further comprises a step of:

(3) culturing the human cell aggregate comprising i) hypothalamus neuroepithelial tissue, and ii) hypophysial placode and/or Rathke's pouch in suspension in a serum-free medium comprising a substance activating or enhancing the Shh signal pathway to induce differentiation of hypophysial placode and/or Rathke's pouch into pituitary hormone-producing cells, thereby obtaining a human cell aggregate comprising an adenohypophysis.

5. The production method according to claim 4, wherein the medium used in step (3) further comprises FGF2.

6. The production method according to claim 4 or 5, wherein the medium used in step (3) further comprises a Notch signal inhibitor.

7. The production method according to claim 6, wherein the Notch signal inhibitor is DAPT.

8. The production method according to any one of

claims 4 to 7, wherein the pituitary hormone-producing cell is at least one selected from the group consisting of growth hormone (GH)-producing cell, prolactin (PRL)-producing cell, and adrenocorticotropic hormone (ACTH)-producing cell.

9. The production method according to any one of claims 1 to 8, wherein the bone morphogenetic protein signal transduction pathway activating substance is BMP4.

10. The production method according to any one of claims 1 to 9, wherein the substance activating or enhancing the Shh signal pathway is SAG.

11. The production method according to any one of claims 1 to 10, wherein the hypothalamus neuroepithelial tissue is a ventral hypothalamus neuroepithelial tissue.

12. The production method according to any one of claims 1 to 11, wherein the pluripotent stem cells are embryonic stem cells or induced pluripotent stem cells.

13. The production method according to any one of claims 1 to 12, wherein the culturing in suspension is performed in the absence of feeder cells.