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Decidualization of the human endometrium

Hidetaka Okada | Tomoko Tsuzuki | Hiromi Murata

Department of Obstetrics and Gynecology, Kansai Medical University, Osaka, Japan

Correspondence
Hidetaka Okada, Department of Obstetrics and Gynecology, Kansai Medical University, Hirakata, Japan.
Email: hokada@hirakata.kmu.ac.jp

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Abstract

Background: Decidualization of the human endometrium, which involves a dramatic morphological and functional differentiation of human endometrial stromal cells (ESCs), is essential for the establishment of a successful pregnancy. Decidualization results from a complex interplay of transcription factors, morphogens, cytokines, cell cycle regulators, and signaling pathways.

Methods: Based on a literature review, the regulation of, and the molecular mechanisms involved in, the decidualization of the endometrium are described.

Main findings: Progesterone, together with proteins that are regulated by progesterone and/or cyclic adenosine monophosphate, including homeobox A10, forkhead box O1, signal transducers and activators of transcription, and heart and neural crest derivatives expressed transcript 2, forms a critical network for ESC decidualization and is a prerequisite to successful implantation. Decidualized ESCs contribute to the microenvironment at the feto–maternal interface and its direct or indirect influence on extracellular matrix remodeling, regulation of the local immune response, anti-oxidative stress, and angiogenesis (vascular maturation). Impairment of this process is associated with a variety of pregnancy disorders, including infertility, recurrent miscarriages, and uteroplacental disorders.

Conclusion: A deeper understanding of the process of decidualization is expected to provide new insights into the fields of reproductive biology and reproductive medicine.

KEYWORDS

decidualization, endometrial stromal cells, endometrium, heart and neural crest derivatives expressed 2, progesterone

1 | INTRODUCTION

The human endometrium undergoes extensive growth in a cyclic manner and is regenerated nearly 450 times in a woman's lifetime.[1,2] It undergoes regular cycles of menstruation, menstrual repair, proliferation, and secretory differentiation, which are controlled by a sequential, carefully timed interplay of female sex hormones during the menstrual cycle. Local levels of autocrine and paracrine molecules vary during the menstrual cycle and they have profound roles in uterine function.[3,4] The endometrial cycle consists of two dominant phases: the proliferative phase, which follows menstruation and precedes ovulation, and the secretory phase, which occurs after ovulation. During the secretory phase, the endometrium transforms into a receptive tissue that is suitable for implantation.

The endometrium is a complex multicellular tissue that undergoes dynamic remodeling to establish a microenvironment that is suitable for supporting a pregnancy.[5,6] Pregnancy is a complex process that comprises separate events, including decidualization, implantation, and

placentation.[7] These processes are primarily coordinated by the ovarian steroids, estradiol (E2) and progesterone, which communicate with signals from the endometrium and embryo to establish the chronological transitions.[8]

Decidualization of the human endometrium involves a dramatic morphological and functional differentiation of human endometrial stromal cells (ESCs). The human decidua is formed routinely and is shed off in the absence of an embryo in the endometrium.[9] Once the luminal epithelium is breached, the embryo is rapidly embedded in the decidual stroma.[10] The decidual reaction plays a central role in the establishment of a pregnancy and continues throughout the pregnancy. This process is one of the most critical and remarkable events that occurs within the human endometrium during pregnancy. The impairment of this process leads to a variety of pregnancy disorders, including infertility, recurrent miscarriages, and uteroplacental disorders.[11–13] Despite significant advances in assistive reproductive technology (ART), many couples experience infertility as a result of failed implantation of the fertilized embryo into the uterus and the subsequent loss of pregnancy. The implantation rates in ART remain low, even with high-quality embryos, emphasizing the importance of an impaired decidualization process as a major cause of pregnancy failure and infertility. Deepening the understanding of the intricate mechanisms of decidualization will aid in alleviating the many problems that are associated with infertility and improve the success rates of ART. The authors believe that research in this field should focus now on expanding the understanding of the decidualization of the human endometrium.

2 | DECIDUALIZATION AND DECIDUAL STRUCTURE

Decidualization is the differentiation of elongated, fibroblast-like mesenchymal cells in the uterine stroma to rounded, epithelioid-like cells during the menstrual cycle and pregnancy.[14] This morphological change is initiated during the mid-secretory phase of the menstrual cycle as a result of elevated progesterone levels and begins with stromal cells surrounding the spiral arteries in the upper two-thirds of the endometrium, regardless of the presence or absence of a conceptus. Human decidualization begins approximately 6 days after ovulation, at the onset of the putative window of implantation.[15] The process is characterized by morphological change in the ESCs, secretory transformation of the uterine glands, an influx of specialized uterine natural killer (uNK) cells, and vascular remodeling to support the maternal blood supply to the growing conceptus.[10,16] Decidualized ESCs, which provide nutrition for the implanting blastocyst, are the main cell type in the decidua.[17] Ultrastructural studies of human decidual cells indicate the characteristics of the epithelioid cells: enlarged and rounded nuclei, increased numbers of nucleoli, dense membrane-bound secretory granules, cytoplasmic accumulation of glycogen and lipid droplets, and the expansion of the rough endoplasmic reticulum and Golgi complex.[15,18]

3 | OVARIAN STEROID HORMONE CONTROL DECIDUALIZATION

Decidualization occurs in response to elevated levels of the ovarian steroid hormones, E2 and progesterone.[19] Hormonal changes are required in order to support the differentiation that is necessary for implantation during the menstrual cycle.[20] Estradiol plays an important role in the expression of the progesterone receptor (PR), which permits the endometrium to respond to the progesterone in the secretory phase.[21,22] Progesterone is a key factor in the establishment and maintenance of pregnancy.[19] Circulating progesterone increases during the secretory phase of the menstrual cycle and remains elevated during pregnancy. Inadequate levels of postovulatory progesterone are associated with infertility and recurrent miscarriages.[23]

Progesterone acts by binding and activating its nuclear receptor, PR, which plays a role in the signaling of stimuli that maintain endometrial homeostasis during the preparation for pregnancy. In humans, PR is highly expressed in the stromal cells during the secretory phase and in pregnancy, whereas its expression in the epithelial cells decreases after ovulation. In mice without a functional PR gene, the endometrium is unable to decidualize, resulting in pleiotropic reproductive abnormalities.[24] Therefore, progesterone signaling via PR is essential for decidualization and is a prerequisite to successful implantation. These findings indicate that progesterone is the master regulator of pregnancy in both humans and mice.

There are two isoforms of PR, PR-A and PR-B, which are generated from alternate transcripts that arise from a single gene via alternative promoter usage. Interestingly, genetic ablation of PR-A, but not PR-B, expression in mice resulted in a uterine phenotype that was similar to that of PR knockout.[25] Therefore, PR-A is the

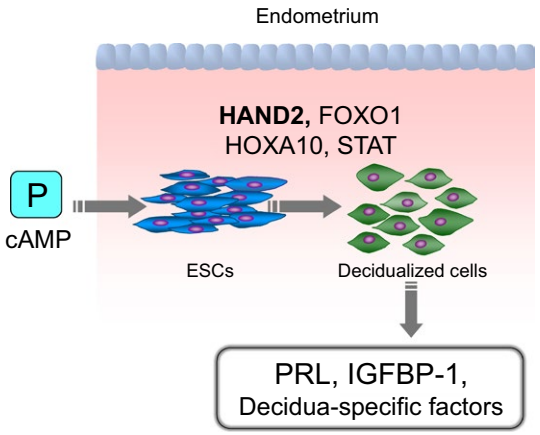

FIGURE 1 Progesterone (P), together with proteins that are regulated by progesterone and/or cyclic adenosine monophosphate (cAMP), including heart and neural crest derivatives expressed transcript 2 (HAND2), forkhead box O1 (FOXO1), homeobox A10 (HOXA10), and signal transducers and activators of transcription (STAT), forms a critical network for the decidualization of human endometrial stromal cells (ESCs). Decidualization involves dramatic morphological and functional differentiation and the expression of decidua-specific factors and decidual markers, such as prolactin (PRL) and insulin-like growth factor-binding protein 1 (IGFBP-1)

major isoform that is involved in the regulation of decidualization in mice. However, in humans, PR-B plays a dominant role during decidualization.[23]

4 | REGULATION OF, AND MOLECULAR MECHANISMS DURING, DECIDUALIZATION

Many studies have investigated the regulation of, and the molecular mechanisms involved in, the decidualization of the endometrium in vitro, using human-cultured ESCs that express the functional PR and estrogen receptor.[26] The treatment of cultured ESCs with progesterone for 12 days triggers the morphological differentiation and expression of the decidual markers, such as decidual prolactin (PRL) and insulin-like growth factor-binding protein 1 (IGFBP-1) (Figure 1).[27,28]

Intracellular levels of cyclic adenosine monophosphate (cAMP) reportedly increase during decidualization after several days of progestin treatment.[29] It is well documented that the ovarian hormones, as well as relaxin, corticotropin-releasing factor, and prostaglandin E2, induce the accumulation of intracellular cAMP.[30,31] In human cell culture systems, cAMP is known as an inducer of decidualization and is associated with the expression of PRL and IGFBP-1 as decidual markers. The decidualization of the ESCs can be stimulated in vitro within a short time frame of ≤3 days by cAMP activation of the protein kinase A-dependent pathway.[15] In cultured ESCs, treatment with cAMP alone increases PRL expression, which is further elevated in the presence of both cAMP and progestin. However, recent studies have demonstrated that several genes in human ESCs are specifically upregulated by progestin, but not by cAMP.[29,32,33] These results suggest that there is an interesting disparity between the progestin and cAMP regulatory pathways during the decidualization of human ESCs.

The identification of the gene expression patterns that are induced by specific hormones provides an insight into the molecular events underlying their diverse and tissue-specific actions. A critical network for ESC decidualization is comprised of progesterone and proteins that are regulated by progesterone and/or cAMP. These include homeobox A10, forkhead box O1 (FOXO1), signal transducers and activators of transcription, as well as heart and neural crest derivatives expressed transcript 2 (HAND2),[30,31,34] which is a transcription factor that is required for the development and growth of the branchial arches, limb buds, and heart. Furthermore, recent reports have described that HAND2 plays an important role in uterine receptivity.[35,36] During the decidualization of human ESCs, progestins increase the HAND2 messenger (m)RNA level in a time- and dose-dependent manner.[37] The authors have demonstrated that small interfering (si)RNA-mediated silencing of HAND2 expression in ESCs during progestin-induced decidualization attenuates both the morphological differentiation and the levels of the decidua-specific factors, including PRL, fibulin-1 (FBLN1), tissue inhibitor of metalloproteinase (TIMP)-3, and interleukin (IL)-15.[37] The HAND2 siRNA effectively suppressed nuclear FOXO1 protein expression as a regulator of decidualization. These results suggest that HAND2 plays a key role in the regulation of the progestin-induced decidualization of human ESCs.

5 | FUNCTIONS OF DECIDUALIZATION

The decidualized endometrium plays essential roles in protecting the embryo from maternal immunological rejection and provides nutritional support for the developing embryo prior to placental formation.[38,39] Decidualization is essential in the coordinated regulation of trophoblast invasion and placental formation and is accompanied by a unique biosynthetic and secretory phenotype.

The major secretory products of decidual stromal cells include PRL and IGFBP-1, two proteins that have been used as markers of decidualization. In the decidual–placental interface, those proteins have been suggested to stimulate trophoblast growth and invasion, to prevent immune rejection, to modulate uNK cell survival, and to promote angiogenesis.[13,15,40] Therefore, they play an important role in decidualization and the control of trophoblast invasion.

Transcriptome and secretome analyses in the past decades have revealed changes in signaling molecules and their intermediates, transcription factors, hormones, growth factors, cytokines, chemokines, adhesion molecules, ligands and receptors, cytoskeletal organization, composition of the extracellular matrix (ECM), ion and water transporters, cell cycle regulators, angiogenic factors, and neuropeptides during decidualization.[5,13,32] Based on the findings of these studies, decidualization has been described as a process of sequential reprogramming of functionally related processes, including ECM organization, cell adhesion, cytoskeletal organization, signal transduction, metabolism, stress responses, cell cycle progression, the inflammatory response, and apoptosis.[28] Thus, the decidualized ESCs within the human endometrium acquire unique biochemical and cellular properties that enable them to support blastocyst implantation. In the following sections will be discussed the role of each of these processes in the preparation of the endometrium for blastocyst implantation, in more detail (Figure 2).

5.1 | Extracellular matrix remodeling

Implantation and placentation in humans involve deep invasion of the trophoblast cells into the endometrial architecture. The decidual cells form the ECM, with which the trophoblast cells interact during invasion and limit the extent of the aggressive invasion of trophoblast cells.[40] Adherens junctions are found between the decidual cells and the arrangement of the gap junctions between these cells might be helpful for trophoblast invasion. The ECM proteins that are produced by the decidualized stromal cells include fibronectin, laminin, type IV collagen, decorin, and heparin sulfate proteoglycans.[4,15,16]

The ECM remodeling is integral to the preparation of the endometrium for implantation and is believed to be under hormonal regulation. In the authors' previous study to reveal the molecular mechanisms that are involved in decidualization, the microarray analysis demonstrated the upregulation of FBLN1 following progestin treatment of 3 day cultures of human ESCs.[41] The FBLN1 is a secreted glycoprotein that is found in association with ECM structures, including fibronectin- and elastin-containing fibers and basement membranes, and it has been implicated in cellular transformation.[42] The FBLN1 plays an essential

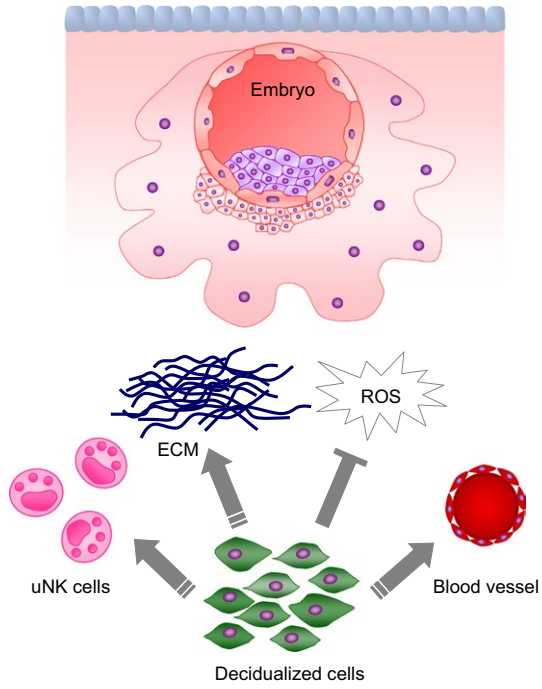

FIGURE 2 Decidualized stromal cells contribute to the microenvironment at the feto–maternal interface and their direct or indirect influence on extracellular matrix (ECM) remodeling, regulation of the local immune response that is mediated by uterine natural killer (uNK) cells, anti-oxidative stress for reactive oxygen species (ROS), and angiogenesis

role in tissue remodeling by affecting cell adhesion, migration, proliferation, and differentiation. It is also a key component of the ECM that is involved in the epithelium-to-mesenchymic transition.[43]

The FBLN1 protein is expressed in the stromal cells of human endometrial tissues and the FBLN1 mRNA levels are higher during the secretory phase than during the proliferative phase.[41,44] Progestin stimulates FBLN1 mRNA levels in a dose-dependent manner in cultured human ESCs.[45] These in vivo and in vitro findings showed that FBLN1 is important in mediating progesterone action in human ESC differentiation. The current authors recently reported that HAND2 is required for progestin-induced FBLN1 mRNA and protein expression in human ESCs.[33] These results suggest that HAND2 is an essential downstream target of the progesterone pathway to induce FBLN1 in ESCs.

The gap junction formation in the stromal compartment is an ultrastructural marker of decidual formation.[46] Recent studies have revealed that decidual morphological changes are associated with the increased expression of connexin-43 (CX43), a major gap junction protein, and that the loss of CX43 expression resulted in an aberrant differentiation of the uterine stromal cells.[18,47] In accordance herewith, it was found that HAND2 knockdown significantly reduced CX43 protein expression in ESCs.[33] These results suggest that HAND2 contributes to the increased CX43 levels that are involved in the formation of gap junctions during decidualization.

Trophoblast invasion requires proteolytic degradation and remodeling of the decidual ECM. Matrix metalloproteinases (MMPs) that are secreted by trophoblasts are involved in this ECM degradation.[40,48] The decidua at the same time produces TIMPs to antagonize the proteolytic activity of MMPs and to limit trophoblast invasion in order to protect the endometrium from invasive damage. Thus, the decidua has been suggested to create a physical and biochemical barrier that limits invasion.

5.2 | Regulation of the local immune response

The decidua plays an integral role in ensuring immune tolerance toward the semi-allogeneic fetal–placental unit and protects the conceptus from the mother's immune system.[38,49] Decidual ESCs acquire specific functions that are related to the development of maternal immune tolerance, as well as to the recognition, selection, and acceptance of the allogeneic embryo.[50] The physiological mechanisms are mediated by immune cells, particularly uNK cells and regulatory T cells, which increase in number during early pregnancy.[51,52]

The uNK cells are the predominant immune population and represent ~70% of all leukocytes in the endometrium during the secretory phase and in early-pregnancy deciduas.[51,53] The uNK cells are non-cytotoxic and have non-immune functions during the first trimester of pregnancy, including tissue remodeling, angiogenesis, and control of trophoblast invasion.[54] In mice, uNK cells play a key role in regulating endometrial vascular remodeling at the implantation site.[55] They contribute to the pregnancy by increasing the blood flow at the feto–maternal interface and by facilitating trophoblast migration.[56,57] The main role of the uNK cells is the secretion of interferon-γ and angiogenic factors, including vascular endothelial cell growth factor (VEGF) and angiopoietins (ANGPTs). The uNK cells and other leukocytes in the endometrium do not express PR.[58] Therefore, progesterone indirectly promotes the accumulation and differentiation of uNK cells via cytokines or other soluble factors that are produced by ESCs, as the latter strongly express PR. The activation and survival of uNK cells have been associated with IL-15 in the human endometrium.[59]

The level of IL-15 mRNA in the endometrium significantly increases during the secretory phase, in comparison with the proliferative phase.[60] The IL-15 protein has been reported to localize in ESCs during the secretory phase and in the glandular epithelial cells during the proliferative phase. Recent micro-array-based studies that investigated differential gene expression have revealed that IL-15 is upregulated in the human endometrium during the receptive phase.[61] During progesterone-induced decidualization, the ESCs induce IL-15 mRNA expression and protein secretion that is further enhanced in the presence of E2, although the addition of E2 alone to the culture medium cannot stimulate IL-15 production.[62] These results suggest that IL-15 production in ESCs is under the control of progesterone and E2 in the process of decidualization and that the ESCs produce IL-15 that is involved in regulating the proliferation and function of the uNK cells.[63] Taken together, these observations indicate that extensive cross-talk takes place between the ESCs and immune cells.

Recent studies have demonstrated that decidualized ESCs act both as key gatekeepers and as chief modulators of the local immune

cells.[38] Decidualized ESCs contribute to the micro-environment and directly or indirectly influence immune cell recruitment, distribution, and function.[39,49] Furthermore, ESC decidualization is decisive in transforming the decidua into a receptive implantation site for natural embryo selection and for achieving immune acceptance of the allogeneic fetus.

5.3 | Anti-oxidative stress

Oxidative stress is defined as an increase in reactive oxygen species (ROS), such as superoxide and hydrogen peroxide, due to increased production or reduced metabolism. The ROS are involved in normal cellular metabolism and are continuously generated by the cells in the endometrium.[64] The feto–maternal interface is defined as the interaction between the decidualized endometrium and the invasive extravillous trophoblast cells. The interface is exposed to extensive changes in oxygen tension during pregnancy and induces a lot of intracellular ROS.[65]

Decidualized ESCs encapsulate and enclose the embryo and their noteworthy resistance to oxidative cell damage assures that the pregnancy is protected against these environmental stressors.[15] Actually, decidualized ESCs are remarkably resistant to oxidative cell death, compared with undifferentiated ESCs.[66] The ROS generation is counteracted by the action of anti-oxidant enzymes, such as superoxide dismutases (SODs), that convert it to hydrogen peroxide. Intensive immunostaining for copper, zinc, and manganese-SOD has been found in decidualized ESCs in early pregnancy.[67] Progesterone drives the expression of serum- and glucocorticoid-inducible kinase-1 (SGK1) in the decidualizing stromal cells.[68,69] In pregnancy, endometrial SGK1 activity safeguards the decidual–placental interface against oxidative stress signals that are generated in response to intense tissue remodeling, the influx of inflammatory cells, and dynamic changes in local perfusion and oxygen tension. These findings suggest that endometrial decidualization regulates embryo invasion and tissue homeostasis and presents resistance to oxidative stress.

5.4 | Angiogenesis (vascular maturation)

Vascular maturation is known to occur during the secretory phase of the menstrual cycle, which is regulated by progesterone.[70,71] The vascular system has critical roles in homeostasis, immune defense, oxygen transport, nutrition, excretion, and fluid balance.[72–74] Decidualized ESCs support the remodeling and development of the endometrial vasculature that plays a critical role in embryonic growth and survival. The physiological changes in the endometrium during the menstrual cycle are associated with profound angiogenesis in response to the female sex hormones.[75,76]

Although endometrial angiogenesis is under the hormonal control of E2 and progesterone, these hormones act indirectly via a lot of other regulators. Actually, the complex processes of angiogenesis in the endometrium are tightly controlled by angiogenic and anti-angiogenic factors in a system that can probably be turned on and off within a short time.[74,77,78] Several angiogenic factors in the human endometrium have been identified that play important roles in physiological angiogenesis.[79-82] The important regulators for endometrial angiogenesis include VEGF, ANGPTs, fibroblast growth factor, thrombospondin, relaxin, adrenomedullin, prostaglandins, prokineticins, angiogenin, and stromal cell-derived factor 1.[83-89]

The VEGF is a key mediator of physiological and pathological vascular remodeling.[76,90,91] It can stimulate the proliferation and migration of endothelial cells, as well as vascular permeability.[92,93] This substance plays important roles in the physiological regulation of endometrial angiogenesis.[94] Its actions are essential in the normal proliferation of the endometrium and for vascular permeability in implantation.[95] The VEGF knockout mice resulted in implantation failure and abortion due to poor vascular network development in the endometrium.[96] Female sex hormones have been shown to regulate VEGF mRNA and protein expression in human ESCs.[97-99]

The ANGPTs have been identified as ligands for Tie2, which is a receptor tyrosine kinase that is specifically expressed on endothelial cells.[100] The ANGPTs comprise a second key group of promoters of angiogenesis and vessel remodeling in the endometrium and interact with VEGF.[101] The ANGPTs contain four subtypes, of which ANGPT1 and ANGPT2 are the best characterized.[102] Although ANGPT2 mainly is observed in the glandular epithelium in the secretory endometrium, ANGPT1 is expressed in a large part of the stroma surrounding the blood vessels[101] and plays important roles in the maintenance and stabilization of the mature vessels, whereas ANGPT2 antagonizes the stabilizing ability of ANGPT1 by competitively binding to Tie2. Therefore, the balance between ANGPT1 and ANGPT2 expression is important for the stabilization and development of blood vessels.[103-105] Progestins have been found to attenuate ANGPT2 production and sustain the level of ANGPT1, resulting in a reduction of the ANGPT2/ANGPT1 ratio.[84] Vascular maturation in the endometrium is under the control of progesterone during the luteal phase. The dominance of ANGPT1 and the consequent lower ANGPT2/ANGPT1 ratio following the treatment of ESCs with progestins appear to favor the maturation and stabilization of the developed vessels in the endometrium.

6 | CONCLUSION

Decidualization is controlled by complex interactions of transcription factors, cytokines, and signaling pathways. Progesterone is an essential regulator of decidualization and a prerequisite for successful blastocyst implantation. A critical network for the decidualization of ESCs is comprised by progesterone and its downstream molecules, including FOXO1 and HAND2. Local autocrine and paracrine molecules vary during decidualization and it has been suggested that they play various roles in endometrial function. Decidualized ESCs contribute to the micro-environment in the human endometrium and have direct and indirect influences on ECM remodeling, local immune response regulation, anti-oxidant responses, and angiogenesis (Figure 2). The impairment of the decidualization process is associated with infertility, recurrent miscarriages, and uteroplacental disorders. Therefore, knowledge regarding decidualization is

expected to aid in improving the success rates in ART and to lay a foundation for the development of new treatments in reproductive clinical practice.

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Conflict of interest: The authors declare no conflict of interest. *Human rights statement and informed consent*: This article does not contain any study with human participants that have been performed by any of the authors. *Animal studies*: This article does not contain any study with animal participants that have been performed by any of the authors.

ORCID

Hidetaka Okada http://orcid.org/0000-0002-7932-6999

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