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REVIEW

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# Novel tissue interactions support the evolution of placentation

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## Abstract

Organ development occurs through the coordinated interaction of distinct tissue types. So, a question at the core of understanding the evolution of new organs is, how do new tissue-tissue signalling networks arise? The placenta is a great model for understanding the evolution of new organs, because placentas have evolved repeatedly, evolved relatively recently in some lineages, and exhibit intermediate forms in extant clades. Placentas, like other organs, form from the interaction of two distinct tissues, one maternal and one fetal. If each of these tissues produces signals that can be received by the other, then the apposition of these tissues is likely to result in new signalling dynamics that can be used as a scaffold to support placenta development. Using published data and examples, in this review I demonstrate that placentas are derived from hormonally active organs, that considerable signalling potential exists between maternal and fetal tissues in egg-laying vertebrates, that this signalling potential is conserved through the oviparity-viviparity transition, and that consequences of these interactions form the basis of derived aspects of placentation including embryo implantation. I argue that the interaction of placental tissues, is not merely a consequence of placenta formation, but that novel interactions form the basis of new placental regulatory networks, functions, and patterning mechanisms.

**KEYWORDS**
implantation, placenta, research highlights, signalling, uterus, viviparity

## 1 | INTRODUCTION

### 1.1 | Evolution of new organs

When Darwin grappled with the implications of evolution, he famously considered, what is the purpose of half an eye (Darwin, 1859). The eye might appear perfectly crafted, in place, to perform its proposed function, but like organisms themselves, organs are also the product of evolution. Understanding how organs originate is difficult because organs typically evolved a long time ago, individually evolved a limited number of times in all of history, and are facilitated by a complex series of events. To overcome this problem, researchers have looked at the molecular biology of organogenesis, models where organs have arisen multiple times independently, lineages which contain transitional states, and systems where closely related taxa lack or have gained that organ (Griffith & Wagner, 2017; Oakley & Speiser, 2015). From these studies an interesting observation has been made, that organs both develop and perhaps originate from the interaction of distinct biological tissues.

### 1.2 | Interactions as a driver of organ development

By day 16 of human pregnancy, the embryo is little more than 3 distinct tissue layers, endoderm, mesoderm, and ectoderm (Gilbert & Barresi, 2016). From these layers, regional specialisation occurs through the co-ordinated interaction of the layers themselves. As development progresses, new coordinated interactions of more derived tissue unfold, and organogenesis occurs through these interactions. Interaction of distinct tissues is an important component of development, because it offers a convenient mechanism for conveying temporal and positional information between neighbouring cells.

  

For example, the development and placement of each tooth is achieved by interactions of the oral epithelium with neighbouring mesenchymal cells of the developing dental papilla (Sadier, Santana, & Sears, 2020; Slavkin, Snead, Zeichner-David, Jaskoll, & Smith, 1984), an interaction that occurs only at this place and time in development. Signalling between these two differentiated tissues, contains sufficient temporal and locational information for organ patterning.

Tissue-tissue signalling is the crux of development, and to understand how new organs originate, we need to know how new signalling networks arise. While interactions offer a convenient system for recognising the location and temporal development within an organism, new interactions of tissues offer a unique opportunity for new signalling networks to manifest simply as a consequence of the new interaction. New tissue interactions can arise through a variety of developmental changes, including the removal of physical barriers so that tissues are apposed in novel ways, and changes in the timing of development, so that tissues that may have been temporally separated now come into contact. In this way, structural rearrangements in development can been seen as new opportunities for tissue signalling to arise.

### 1.3 | The placenta as a model for organ evolution and new signalling potential

While understanding the evolution of most vertebrate organs is difficult due to their ancient history, the placenta is a more recently evolved organ, which has been derived more than 150 times in fish, amphibians, reptiles, and mammals (Blackburn, 2015). Placentas are an organ formed from the fusion or apposition of parental and fetal tissues for physiological exchange (Mossman, 1937). The placenta is a unique organ to study the origin and evolution of complexity because placentas have evolved multiple times independently, have been derived relatively recently in some taxa, and exist in intermediate forms in extant species (Blackburn, 2015; Cornetti et al., 2017; Griffith & Wagner, 2017; Laird, Thompson, & Whittington, 2019).

The evolution of placentation starts with the evolution of pregnancy, where a parent, retains the developing embryo internally until development is complete. Therefore, a consequence of pregnancy, is a new proximity of parental and fetal tissues. The signalling dynamics that change through the evolutionary process can be understood in three stages (Figure 1). In the ancestral condition maternal and fetal tissues are temporally separated because most of development happens outside the mother and spatially separated because of the presence of an eggshell that inhibits maternal–fetal interactions. Therefore, any signalling that occurs within the fetus is confined to the fetus and similarly for the mother (Figure 1a). The evolution or pregnancy requires egg-retention and due to the requirements of gas exchange for the embryo, eggshells are typically greatly reduced. This means that signals produced by the fetus can now spuriously diffuse into the maternal tissues and impact uterine tissue development and vice-versa (Figure 1b). Selection is likely to act on the new spurious signalling dynamics and with time, we would expect to see a derived signalling network that uses the spuriously signalling network as a scaffold to drive normal placental development (Figure 1c). In this way, placentation arises from a novel interaction of two tissues, and is supported by the interaction of the two tissues.

In this review, I evaluate three key predictions from the model using existing data: (a) that the tissues from which placentas are derived are ancestrally active signalling tissues; (b) that parental tissue contains the receptors necessary to receive signalling molecules produced by the fetal membranes; and that (c) maternal–fetal interactions have been assimilated into the placental development program.

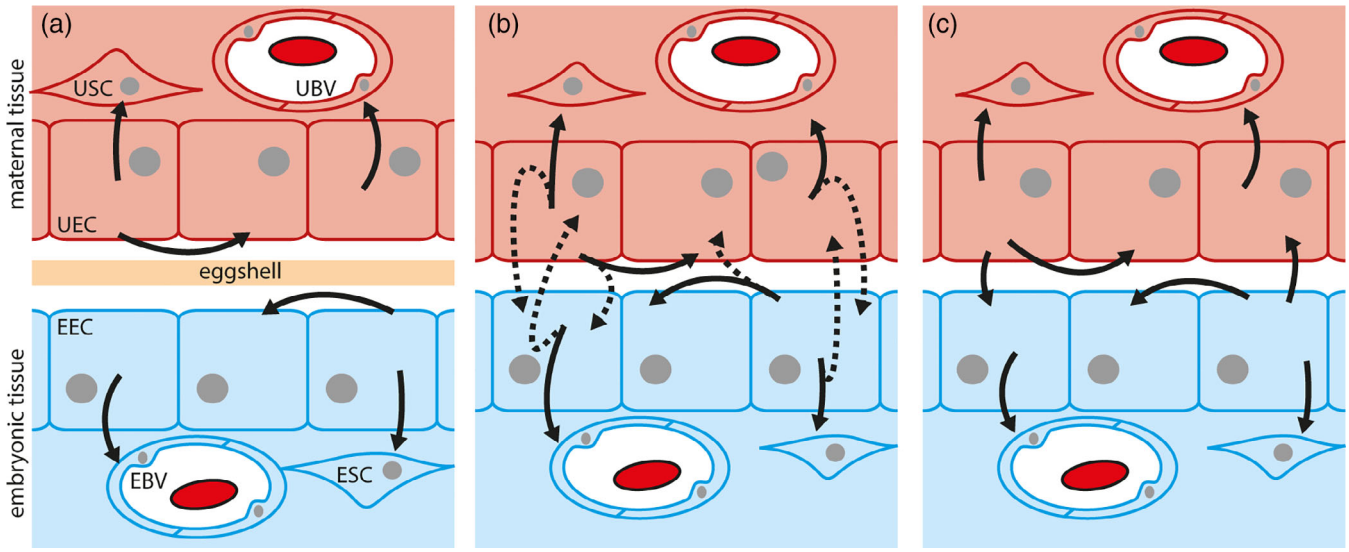


**FIGURE 1** Signalling dynamics through the oviparity-viviparity transition. In the ancestral condition (a) signals produced in the maternal tissue (red) and fetal tissues (blue) are spatially and temporally separated. Once viviparity evolves (b) the shell is lost and now fetal signals can spuriously diffuse into maternal tissues and impact on maternal tissue development and vice versa. Selection on this spurious signalling dynamic will result in a derived maternal–fetal signalling network (c), optimised for placental development. Modified from Griffith and Wagner (2017)

## 2 | ASSESSING THE ROLE OF NOVEL INTERACTION IN THE EVOLUTION OF THE PLACENTA

### 2.1 | Placentas are derived from actively signalling tissues

In amniotes (reptiles, birds, & mammals), placentas (when present) are derived from a limited set of tissues, the uterus of the mother, and a series of embryonic membranes of the fetus. These fetal tissues include the chorioallantoic membrane, a fusion of the embryonic chorion and allantois, and the yolk sac membrane, a fusion of the chorion and omphalopleure. In fishes, placentas are derived from a greater diversity of structures. In poecilids, placentas form from the apposition of fetal tissues with the ovarian follicle wall. In Syngnathids (pipefish and seahorses) placentas form from the apposition of the fetal membranes and skin tissue, which in some species is modified to form a pouch. While work has been done to investigate molecular aspects of placentation in fishes (Jue, Foley, Reznick, O'Neill, & O'Neill, 2018; Whittington, Griffith, Qi, Thompson, & Wilson, 2015), transcriptome wide examination of maternal and fetal tissues separately has only been performed in squamates and mammals (Griffith & Wagner, 2017).

The chorioallantois, which forms the definitive placenta in humans, is a thin vascularised membrane that lines the internal surface of the eggshell in oviparous amniotes. This tissue facilitates gas and water exchange between the fetus and the external environment. While the chorioallantois is known to be an endocrine organ in placental animals like ourselves, the tissue is a hormone producing organ in oviparous amniotes as well. In chickens and turtles, the chorioallantois can synthesise progesterone from precursor molecules (Albergotti, Hamlin, McCoy, & Guillette Jr., 2009; Cruze, Hamlin, Kohno, McCoy, & Guillette Jr., 2013). Alligator chorioallantoic membranes also produce mRNA and proteins required for steroid hormone synthesis, including progestins, estrogens, and androgens (Cruze, Kohno, McCoy, & Guillette, 2012). In addition to its role in steroid synthesis, transcriptomic studies suggest that the chorioallantoic membrane of both, egg laying and live bearing amniotes, is capable of synthesising a suite of other hormones and signalling molecules (Griffith, Brandley, Whittington, Belov, & Thompson, 2017). These include growth hormones, angiogenic factors, as well as WNT and BMP signalling molecules. Why this tissue, which sits distally to the embryo, has endocrine functions in addition to its role in general egg homeostasis is not known, however, as it is the closest living tissue to the external environment, it may have a role in sensing environmental change and adjusting development to cope with that change accordingly.

### 2.2 | The potential for maternal–fetal communication is not a derived feature of pregnancy

The production of signalling molecules in the placenta, and the tissues from which they are derived is only half the story, for a signal to be important, target cells need to have receptors to receive those signals. In eutherian mammals, many fetal-maternal signalling dynamics are well understood. One of the best studied, is the dynamics of progesterone signalling to shift the uterus to a state that can support gestation (Chavan, Bhullar, & Wagner, 2016).

In humans, progesterone is a critical hormone that facilitates the extension of pregnancy. Initially, progesterone is produced by the corpus luteum after ovulation, but after 6–8 weeks, luteal production declines and the trophoblast takes over (Tuckey, 2005). Progesterone receptors are wide spread in the human uterus, where they play a role in decidualisation of the endometrium (Gellersen & Brosens, 2003) and the suppression of uterine contractions in the myometrium (Mesiano et al., 2002). Outside of mammals, progesterone is a key regulator of uterine development as well. In archosaurs, most of our understanding on the maternal side of gestation comes from work in birds. In chickens, progesterone receptors are found in luminal epithelial, glandular, and stromal cells of the uterus (Gasc et al., 1984). In the magnum (the part of the oviduct responsible for egg white deposition), progesterone signalling is necessary for the secretion of key components of the egg white, ovalbumin and avidin (Sah & Mishra, 2018). Loss of progesterone receptors in the oviduct is associated with ageing in hens, and post-laying hens lose progesterone receptor isoforms from every oviductal cell type (González-Morán, 2016). Progesterone receptors have also been identified in alligators (Vonier, Guillette, McLachlan, & Arnold, 1997) and turtles, where progesterone reduces uterine contractions (Giannoukos & Callard, 1996). In squamates, there is a lot of evidence that progesterone is important for regulating uterine activity. Progesterone receptor abundance in the oviduct of lizards and snakes is regulated throughout the reproductive window (Kleis-San Francisco & Callard, 1986; Paolucci & Di Fiore, 1994). In the viviparous skink *Pseudemoia entrecasteauxii*, blocking the progesterone receptor (which is expressed in multiple uterine cell types) with mifepristone leads to pregnancy failure in early gestation (Biazik, Parker, Murphy, & Thompson, 2012). Progesterone receptors have been associated with reproductive timing and development of the oviduct in every squamate in which it has been examined (Custodia-Lora & Callard, 2002). Given the diversity of systems that have been examined it appears that progesterone is produced by fetal membranes ubiquitously in amniotes, and progesterone appears to act ubiquitously on the oviduct to support reproductive development. Therefore, under the novel tissue interaction model the mere reduction of shell thickness in a species with some embryonic development in utero (which includes mammals and squamates) may be sufficient to extend gestation in amniotes, as fetal progesterone production acts to prevent myometrial contractions and maintain the uterus in a pregnancy like state.

Progesterone is not unique as a hormone that might eventuate in maternal–fetal signalling through novel tissue interactions. While targeted analysis of hormone and receptor localisation to maternal and fetal placental tissues has focussed heavily on steroid hormone dynamics (Murphy & Thompson, 2011), new transcriptomic analyses allow us to look more broadly at what potential there may be for signalling in other pathways. One exciting contrast can be made

between the closely related oviparous (*Lampropholis guichenotti*) and viviparous (*Pseudemoia entrecasteauxii*) skinks for which we have extensive gene expression data from published uterine and chorioallantoic membrane transcriptomes (Griffith, Brandley, et al., 2017; Griffith, Brandley, Belov, & Thompson, 2016). By looking at the ligand and receptor genes expressed above a transcript per million threshold, we can build a map of the potential for maternal–fetal signalling between these two tissues (Figure 2). In the viviparous species (Figure 2b) maternal and fetal tissues express genes responsible for the production of a suite of ligands and receptors, offering these tissues significant potential for maternal–fetal signalling (signalling arrows). In the oviparous species (*L. guichenotti*), although the uterus and fetal membrane never come into contact, we can build a similar a theoretical signalling map (Figure 2a). The number of potential signalling paths in the oviparous (97 ligand/receptor connections) and viviparous (104 ligand/receptor connections) species do not differ substantially. Of these ligand receptor connections 62 are conserved between both species, suggesting that just over half of the signalling potential between maternal and fetal tissues in the placental skink is ancestral to the tissues from which the placenta is derived. These data suggest that the mere apposition of maternal and fetal tissues (which is essentially a consequence of the evolution of viviparity) is likely to lead to new signalling dynamics at the placenta interface that could be used to build a derived maternal–fetal signalling program.

Many of the conserved ligands and receptors expressed in both our oviparous and viviparous skinks are important for placental signalling in live bearing mammals. The conserved signalling pathways between oviparous skinks, viviparous skinks, and viviparous mammals include prostaglandin signalling (Griffith, Brandley, et al., 2017), wnt signalling (Sonderegger, Pollheimer, & Knöfler, 2010), and activin/inhibin signalling (Jones, Salamonsen, & Findlay, 2002). Given the extensive potential for signalling in the ancestral oviparous condition and the conservation of this signalling in viviparous species, I suggest that the potential for molecular communication between maternal and fetal tissues is not a derived feature of placentation, but rather a consequence of changing the timing of reproductive processes (egg retention) and a decrease in the barriers that prevent interactions (loss of an eggshell).

## 2.3 | The consequences of maternal fetal interactions have been coopted into derived aspects of mammalian pregnancy

The dynamics of mammalian pregnancy have been studied to a much greater extent than for squamates or fish. Mammalian placentation is dependent on maternal–fetal signalling. Signalling is needed to establish implantation, to regulate placental nutrient transport, and to initiate parturition. In eutherian mammals, embryo implantation requires

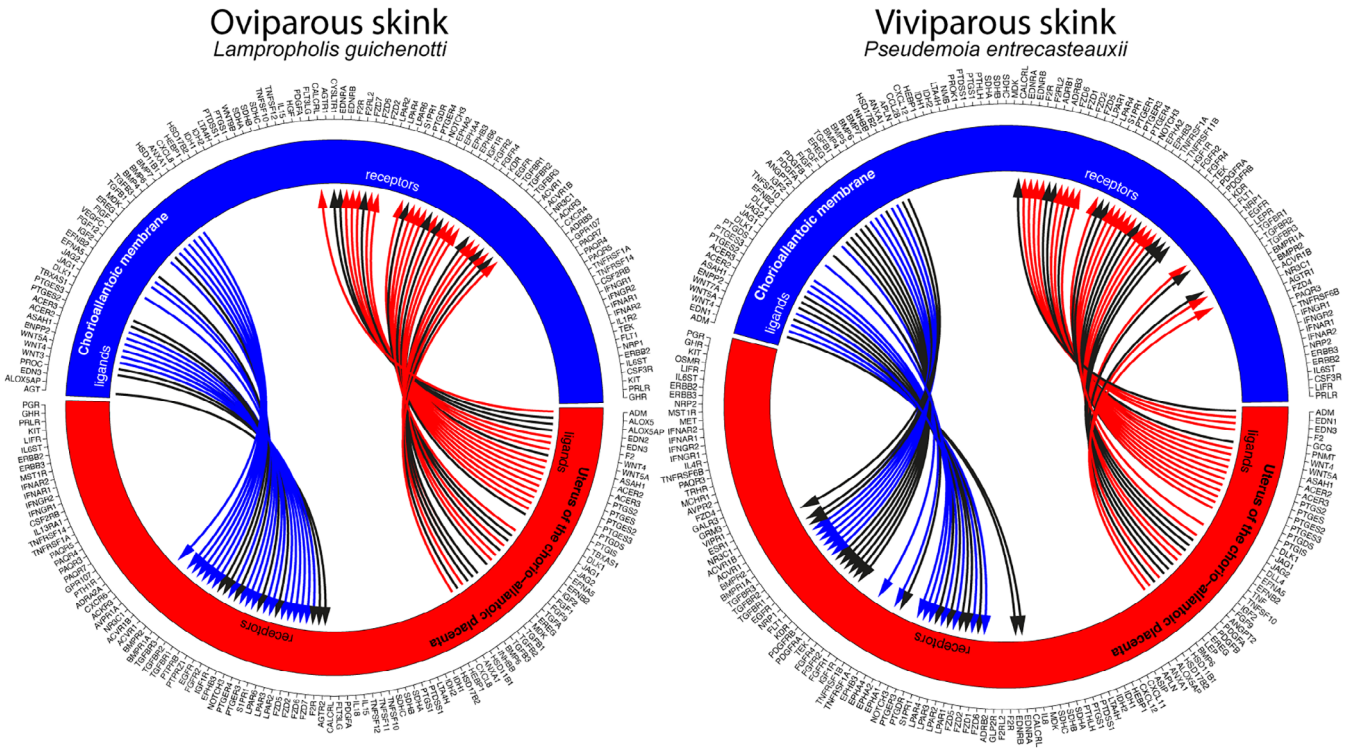


**FIGURE 2** Signalling interaction map, showing the potential pathways of signalling between the chorioallantoic membrane and uterus of the egg laying, common garden skink (*Lampropholis guichenotti*) and the livebearing, southern grass skink (*Pseudemoia entrecasteauxii*), built from published gene expression data. Genes are included if their mean expression was greater than 15 transcripts per million (TPM). Black arrows represent signalling pathways that are unique to each species, while coloured arrows represent shared signalling pathways between both species

inflammatory signalling, this includes the production of pro-inflammatory cytokines (e.g., tumour necrosis factor and interleukin 6) and Prostaglandin E2 (Kover, Liang, Andrews, & Dey, 1995; Mor, Cardenas, Abrahams, & Guller, 2011; Vilella et al., 2013). While suppression of inflammatory signalling during the implantation window can lead to early pregnancy loss (Li, Liu, & Odouli, 2003), the presence of inflammation through the bulk of pregnancy is associated with both miscarriage and pre-term birth. Until recently, understanding why inflammation is involved in implantation (a normal developmental process, rather than a coordinate response to injury or infection) has persisted as a mystery (Chavan, Griffith, & Wagner, 2017).

Comparisons of maternal–fetal attachment between eutherians and grey short-tailed opossum show that embryo attachment is likely an inflammatory process in all live bearing mammals (Chavan et al., 2017; Griffith et al., 2017). The nature of the inflammatory signalling that occurs in the opossum is consistent with it being induced as a result of tissue damage by the fetal membranes, perhaps as a result of the extensive production of proteases, which are used to degrade the shell coat for hatching (Griffith, Chavan, et al., 2017). Further, the inflammatory signalling is only induced by the presence of an embryo (Griffith et al., 2019), and not as a result of normal ovarian cycling as is seen in some eutherians (Griffith et al., 2018; Liu, 2017). Together these findings support the idea that embryo implantation evolved from an inflammatory maternal–fetal interaction that occurred in the first live bearing mammals.

Despite the presence of inflammatory molecules in eutherian implantation, the consequences of the inflammatory signalling are contained and do not involve the induction of effector immune cells such as neutrophils. The loss of effector immune cells from eutherian implantation is achieved through the modulation of inflammatory signalling by a eutherian specific cell type, decidual stromal cells (Chavan et al., 2020). Despite this modulation of inflammation, many physiological aspects of a normal inflammation pathway are retained, including those that lead to swelling, oedema, and angiogenesis. These physiological changes are likely important for normal embryo implantation, because they lead to a more pliable endometrium for embryo attachment and greater supply of nutrients and respiratory gasses for embryonic development. As a result, eutherian implantation is built from a scaffold of an inflammatory interaction that occurred in the first live bearing mammals, which has been modified by the suppression of components that were incompatible with the extension of gestation in this group. The retention of inflammatory aspects of maternal–fetal interactions into the normal physiology of eutherian pregnancy, is a clear example of how tissue interactions have shaped the evolution of this new organ, the placenta.

## 3 | FUTURE WORK

The novel tissue interaction model allows us to make important predictions about the evolution of placentation. The model proposes that the signalling that occurs between maternal and fetal tissues in the placenta is dependent on the signalling molecules and receptors produced in the ancestral tissues that the placenta is derived from. Therefore, we would predict that maternal–fetal signalling that occurs in lineages that use different tissues to form the placenta would use a different set of signalling molecules and receptors. To test this prediction, researchers need to look at the signalling dynamics in non-amniotes where a greater diversity of parental and fetal tissues are modified to support placentation. While this data is not currently available, I am confident that with the exciting work developing in this space at the moment, it will be soon.

There has been a lot of work to understand gene expression in whole tissues; however, really understanding the nature of the signalling dynamics requires us to look at a finer scale. New single cell sequencing technologies would allow us to identify the signalling potential of each cell type within a placenta and homologous structures of related oviparous species. This scale would allow us to understand the potential for endocrine, paracrine, and juxtacrine signalling dynamics in placenta development and evolution.

While more work is needed to characterise the potential for signalling, these approaches do not allow us to test the novel interaction model explicitly. However, the model can be tested by looking at the signalling dynamics of manipulatable systems, such as in-vitro culturing of maternal and fetal tissues or cells. There has been considerable work developing explant culturing systems for reptile reproductive tissues (Bennett & Jones, 2002; Guillette, Herman, & Dickey, 1988). Explant cultures, if correctly optimised, might give us an exciting opportunity to look at the impacts of novel tissue interactions on cell dynamics in closely related non-model viviparous and oviparous species. This approach does not rely on the establishment of cell lines, so can be done in a diverse collection of non-model species. Once known signalling pathways have been identified, the importance of these pathways can be explored by supressing the signalling molecules or their receptors.

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### AUTHOR CONTRIBUTIONS

**Oliver Griffith:** Conceptualization; writing-original draft.

### CONFLICT OF INTEREST

The author declares no conflicts of interest.

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### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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