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Review Article

Different Co-Culture Systems Have a Useful Impact on Preimplantation Embryo Development

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Abstract

The production of *in vitro* produced embryos of good morphological quality and viability is a prerequisite for successful assisted reproduction biotechnologies in animal breeding and human. The co-culturing system has been applied to improve preimplantation development that could subsequently resulted in successful pregnancy. There are different types of reproductive and non-reproductive cells that have been used during preimplantation development. The most well-known reproductive cells are those recovered from ovaries (cumulus and granulosa cells), oviduct and endometrium cells. While, in last decade stem cells such as mesenchymal stem cells and murine embryonic fibroblasts that originated from different tissues have been used to support early embryonic development. The positive effect co-culturing system was suggested to be due to direct mechanical cell-to-cell contact that occurred between the dividing embryos embryo and helper cells in addition to secretions of various bioactive biological components like growth factors and scavenging the deleterious byproducts that resulted from embryo metabolism. In current review, we will highlight the effects of different couture systems on embryo development and their suggested mechanisms to exert the beneficial impacts.

Keywords: Oocytes; Embryos; Co-culture; Mode of action

Co-culture Systems Importance

Co-culture system has a supportive effect on embryo normal development by strengthen the embryo ability to overcome any damage occurred in early stage according to several mechanisms include: 1) Detoxifying the culture medium from heavy metal ions by chelation; 2) Secretion of nutrients, substrates and embryotrophic factors like amino acids and growth factors into the medium to induce embryonic genome activation and improve the cell structure [1]; 3) Stabilization of the pH and gases concentrations (CO_2 and O_2) and decreasing the oxygen tension [2].

Co-culture Systems

Different co-culture systems support early embryo development according to the types of the cells such as cumulus cells, granulosa cells, oviduct cells, uterine cell monolayers, liver cell monolayers, chicken skin cell monolayers mouse testicular cell monolayers and monkey kidney cells [3,4].

Pre-antral follicles growth and survival rates increase when co-cultured with mesenchymal cells because its secretions providing some important factors as extracellular matrix proteins (1), high molecular mass proteins (6), basement membrane components [5], Transforming Growth Factor- (TGF-) [6], Fibroblast Growth Factor-7 (FGF-7) and Hepatocyte Growth Factor (HGF) [7]. Moreover, HGF and KGF and Kit Ligand protein (KL) expression indirectly regulate the roles of gonadotropins on follicular development [8]. Fibroblast Growth Factor-7 (FGF-7) suppresses granulosa cells apoptosis and stimulates the growth of cultured rat pre-antral follicles [9].

A specific type of cells known as VERO are kind of epithelial cells derived from the kidney of African green monkey At (*Cerpopithecus aethiops*) and the high oxygen concentration is suitable for VERO culture [10]. High oxygen level (20%), the VERO cells increase the bovine blastocyst rate, total cell number and the ability of blastocyst to be tolerant with cryopreservation [11-13].

Cumulus and Granulosa Cells

Cumulus and granulosa cells have supportive effects through cell to cell communication and selective transport for important nutrients from the culture medium to the developed oocytes and embryos. Moreover, they have the ability to synthesis steroid hormones [14] such as activin [15], inhibin [16], thecal differentiation factor [17], fibronectin [18] may cause enhancement in pre-antral follicles growth and survivability.

Granulosa cells secret many beneficial proteins like Kit Ligand protein, which regulates thecal cells function, proliferation and growth [19].

Human oocytes co-cultured with cumulus cells during *in vitro* maturation caused a significant increase in 8-cell stage embryos after 72 hour compared with oocytes matured in control medium (Mansour et al. [14]. In addition co-culture system has a beneficial impact on human embryos development rates, quality and pregnancy rates which increased by the co-culturing embryos produced by IVF with various cellular monolayers [14,20-26].

Porcine pre-antral follicles co-cultured with cumulus cells from antral follicles with diameter more than 3mm resulted in improvement of growth rates [27]. Porcine cumulus and mural granulosa cells play important role in cumulus cells expansion by producing Cumulus Expansion Enabling Factor (CEEF) *in vitro* [28].

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Oviductal and Uterine Cells

Fertilization and early embryonic development till blastocyst stage occur in the oviduct, which provides the suitable environment for gametes survival, early pregnancy success and can alter the embryo gene expression, epigenetic modification and metabolism [29]. However, the crucial secretions of oviduct such as glycoproteins, amino acids, lactate, and growth factors like Insulin-Like Growth Factor (IGF), Interleukin (IL)-l and Platelet-Derived Growth Factor (PDGF) [2,30], some oviduct secretions are identified as chemokines, cytokines, growth factors and apoptosis regulators [31]. Therefore, to increase the *in vitro* Fertilization (IVF) rate, IVF protocols were developed using co-culture systems with oviduct epithelial cells in sheep [32], cattle [33] and mice [29].

Pre-antral follicles co-cultured with Oviductal Epithelial Cells (OEC) showed a decrease in pre-antral follicles growth and survivability rates due to OEC secretion in oviduct is necessary for embryo development and blastocyst formation [34]. Co-culture embryos with oviduct monolayer resulted in an increase in blastocyst rates at oxygen concentration (20%) compared to oxygen level (5%) [35]. Several studies reported that the effect of co-culture involved also the cells, the morphological changes occur when the cells co-cultured as a monolayer [36,37] which impact on gene expression [38] so as an expected result the effect of co-culture on embryo development may be altered during the co-culture period.

Mode of Action and Molecular Impact of Co-culture

Despite the production of several commercial defined embryo culture media, co-culture systems with different types of somatic cells is still used for preimplantation development in many mammalian species. Taken into consideration that there is interest in application of co-culture either autologous or heterologous systems, the actual mechanism explaining their effects is not yet well established. However, there to suggested mode of actions that are most probable justify action of co-culture; there is no evidence yet to identify the correct mechanism of the co-culture effect. In fact, the mode of action of co-culture systems has been explained largely by two mechanisms [2,39].

The first mode is dependent on the scavenging ability of co-culture system in removing the deleterious components that resulted from embryo metabolism and ameliorating effect of oxidative stress that resulted from *in vitro* the culture conditions (medium, composition, pH, and osmolality and oxygen tension). The second possible mode of co-culture action is dependent on bioactive secretions of helper cells into culture medium or what is called embryo trophic factors. In experiment done in bovine embryos [40-46] produced *in vitro* that were co-cultured with adipose tissue-derived from bovine mesenchymal cells which resulted in increasing blastocyst formation rate and quality as assessed through increased number of total embryo cells and upregulation of metabolism related transcript known as G6PDH and gene regulating embryo differentiating (POU5F1).

Conclusion

In could be implicated that co-culture of mammalian embryos with helper cells could be more beneficial than the traditional cells free system. However, the co-culture system and its conditions should be modified and optimized for each species and type of cells. The co-culture micro environmental conditions should be monitored in order to understand the modulatory potential actions of this system and could be applied in standard way.

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