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A review of avian stem cell therapy: A promising health intervention strategy in poultry systems

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Wafaa A. Abd El-Ghany[1*]

[1]*Poultry Diseases Department, Faculty of Veterinary Medicine, Cairo University, Giza, 12211, Egypt* *http://orcid.org/0000-0003-1686-3831*

Author for correspondence: Wafaa A. Abd El-Ghany – wafaa.soliman@cu.edu.eg

Abstract: Stem cells are multi-lineage cells that can be differentiated into many other types of cells under specific conditions. Mesenchymal stem cells (MSCs) or hematopoietic cells are spindle-shaped cells that mainly originate from the bone marrow and are used in different aspects of tissue engineering. The avian MSCs are also derived from chicken embryos and 1 to 14-day-old chicks. There are many sources from which the avian MSCs could be isolated, including amnion, skin, lungs, cartilage, neurons, adipose tissues, and kidneys. Recently, avian MSCs have been used in different poultry aspects such as treating bone and skin affections, preventing some immunosuppressive viral diseases, and improving gut health. Therefore, this review article spotlights avian MSCs regarding their sources and different applications in the poultry field.

Keywords: Avian mesenchymal stem cells; bone and skin affections; disease prevention; gut health.

1. Introduction

Stem cells have been used in vast aspects, including in cell-based therapy, transgenic studies, tissue engineering and transplantation, and viral vaccine production (Petitte and Mozdziak, 2002; Mozdziak and Petitte, 2004; Khatri and Sharma, 2009; Chen et al., 2016; Dai et al., 2017). Thus, these types of cells can be considered a novel source of avian-derived cell lines for potential therapeutic studies (Nierobisz et al., 2011; Mizuno et al., 2012; Stern et al., 2017). However, stem cells may show unexpected fate under certain environmental conditions (Wagers and Weissman, 2004; Young, 2011).

Mesenchymal stem cells (MSCs) are multipotent cells that are derived from the bone marrow and then differentiated into MSCs of other tissues, including myocytes, osteocytes, chondrocytes, and adipocytes (Prockop, 1997; Ayala-Cuellar et al., 2019). Moreover, MSCs also could be obtained from the kidney, lungs, skin, cartilage, and other tissues (Crigler et al., 2007; Dumas et al., 2008; Li et al., 2016) of many species of animals such as chickens, pets, sheep, and rodents as well as humans (Munoz et al., 2012; Kar et al., 2015; Kumar et al., 2016; Krešić et al., 2017; Nakamura et al., 2020). The MSCs could be used as a model for studying the different developmental and physiological processes of animal species. The application of MSCs has gained attention owing to ethical standards, their potentiality, and their proliferation rate (Golchin et al., 2019).

The MSCs can migrate to the damaged areas via circulation to proliferate, differentiate, and reduce the cell's injury by the synergistic action with small molecules and extracellular vesicles, thus facilitating the healing process (Fu et al., 2019). Therefore, they are regarded as a suitable tool for many researchers working in the fields of regenerative medicine for repairing damaged tissues caused by some diseases, cell transplantation, and production of transgenic tissues in different species (Young, 2011; Nakamura et al., 2013; Kawai et al., 2015; Nitkin and Bonfield, 2015; Oh et al., 2018; Selvasandran et al., 2018; Xu et al., 2018; Kim et al., 2019; Zannetti et al., 2020).

From the abovementioned, this review covers what is currently known about avian MSCs in terms of knowledge about their sources and their different applications in the poultry field.

2. Avian MSCs

The populations of avian MSCs or hematopoietic cells are mostly isolated from the adult bone marrow (Khatri et al., 2009; Li et al., 2009; Young, 2011; Bai et al., 2013), chicken's embryos yolk sac (Young et al., 1993), and 1 to 14-days-old chicks (Khatri et al., 2009; Bhuvanalakshmi et al., 2014). Besides, these cells were obtained from the lungs (Khatri et al., 2010), liver, fat, muscles, and kidney tissues (Chen et al., 2016). These cells can differentiate into Oosteogenic, adipogenic, and chondrogenic cells (Guedes et al., 2014).

Under *in-vitro* environmental conditions, MSCs can adhere to plastic surfaces to express several surface antigens (Dominici et al., 2006), self-renew (Khatri et al., 2009; Calloni et al., 2014), and differentiate into multi-lineage of muscles, adipocytes, cartilages, and osteoblasts (Martin et al., 1998; Wagers and Weissman, 2004; Khatri et al., 2010; Bai et al., 2013; Eleuteri and Fierabracci, 2020). In addition, the MSCs can produce some growth factors and cytokines (secretome) for the hematopoietic process (Majumdar et al., 1998). These cells are plastic adherent and positive for cluster of differentiation (CD) such as CD73, CD90, and CD105 surface antigens, but they lack protein expression such as CD45 and CD34 (Sacchetti et al., 2007; Teresa Conconi et al., 2011; Lin et al., 2013; Cruz and Rocco, 2020). Avian MSCs have furthermore shown an immune-regulatory mechanism and inhibition of different immunological responses (Lyer and Rojas, 2008; Fierabracci et al., 2016). The MSCs in chickens may be used as a feeder layer for primordial germ cells (Li et al., 2019) and thus regulate the immune-regulatory mechanism (Lyer and Rojas, 2008; Fierabracci et al., 2016) for some viral infections such as infectious bursal disease virus (IBDV) which does not proliferate in chicken fibroblast cells (Young et al., 1993; Majumdar et al., 1998; Calloni et al., 2014). Furthermore, MSCs are useful for examining the positive effects of vitamin D3 and calcitriol [1,25- (OH)2D3] administration and the immuno-regulatory mechanism through the co-culture with the pathogens (Gil et al., 2018).

The hematopoietic stem cells have an indispensable role in immunity against important immuno-suppressive avian diseases such as Marek's, leucosis, chicken infectious anemia, and Gumboro (Cui et al., 2009; Khatri and Sharma, 2009; Liu et al., 2016; Gurung et al., 2017; Hosokawa et al., 2020). These cells exist in the bone marrow, interact with other cells and molecules, and create a stroma for the bone marrow niche (Walenda et al., 2011; Zhang et al., 2019). They inhibit the differentiation and maturation into dendritic cells and induction of apoptosis.

The avian MSCs showed many advantages, including availability, robust proliferation, and immuno-regulatory properties, which make them an appropriate model in the field of stem cell work (Svoradova et al., 2021). Recently, the MSCs of the endangered Oravka chicken breed were successfully isolated, cultured, characterized, and cryopreserved in a gene bank, thus making them a valuable genetic resource (Svoradová et al., 2023).

3. Sources of avian MSCs

3.1. Amnion

Amniotic MSCs were isolated from amniotic epithelial cells (Gao et al., 2012). They express transcription factors for keeping the self-renewal and the undifferentiated status. These cells can differentiate into osteoblasts, adipocytes, myocardial cells (Li et al., 2014), neural-like cells, and islet-like cells (Gao et al., 2012). Amniotic MSCs are used in autologous cell therapy and tissue engineering (Li et al., 2014; Mamede and Botelho, 2015; Feng et al., 2016).

3.2. Skin

Avian dermis-derived MSCs/progenitor cells were fibroblast-like cells that were isolated from the dermis of 16-day-old chick embryos (Gao et al., 2013). They could be diverged into different lineages, such as osteocytes, adipocytes, and neural cells, that could be used in stem-cell-based therapy and tissue regeneration research (Chen et al., 2015; Park et al., 2015).

3.3. Lungs

Avian lung-derived MSCs were isolated from 1 to 2-week-old chicks, and they are like those of humans (Lama et al., 2007) and mice (Summer et al., 2007) origins. They are fibroblast-like cells and could be differentiated into osteocytes and adipocytes (Khatri et al., 2010). Moreover, they have immunosuppressive effects via inhibition of T-cell proliferation. Avian lung-derived MSCs are vulnerable to pathogenic viral replication and apoptosis. They are a good source for cell therapy of the lungs (Khatri et al., 2010).

3.4. Cartilage

Avian cartilage-derived MSCs could be isolated from the articular cartilage surface of a 20-day-old chicken embryo. They have a long fusiform or polygon shape (Li et al., 2015) and could be differentiated into adipocytes, osteoblasts, and chondrocytes (Karlsson and Lindahl, 2009; Li et al., 2015). These types of cells are an effective tool for cartilage repair (Baksh et al., 2004; Jayasuriya et al., 2016).

3.5. Neurons

Avian neural MSCs could be obtained from the dorsal ventricular ridges of 10 to 13-day-old chick embryos (Hou et al., 2011). These neural stem and progenitor cells could be proliferated into neurons, astrocytes, and oligodendrocytes (Hou et al., 2011). They may give rise to recent findings in gene therapy, neurogenesis, and tumorigenesis (Bengoa-Vergniory and Kypta, 2015; Covacu and Brundin, 2015; Xu et al., 2016).

3.6. Adipose tissues

Avian adipose-derived stem/progenitor cells of MSCs were found in the abdominal tissues and the inguinal fat pads of 1-day-old chickens (Gong et al., 2011). They are multipotent fibroblast-like MSCs that are able, *in vitro*, to differentiate into adipocytes, mycardiocytes, and osteocytes (Mizuno et al., 2012). These cells are an innovative method in regenerative medicine (Gimble et al., 2007; Mizuno et al., 2012; Kapur et al., 2015; van Vollenstee et al., 2016).

3.7. Kidneys

Avian metanephric MSCs were isolated from 20-day-old duck kidney cells (Chen et al., 2016). These cells are pluripotent and capable of differentiation into three somatic lineages such as epithelial cells, liver cells, and pancreatic cells (Chen et al., 2016). They are applied for tissue engineering and cell transplantation of kidneys (Deans and Moseley, 2000).

4. Different applications of MSCs in the poultry field

The different applications of MSCs in the poultry field are shown in Figure 1.

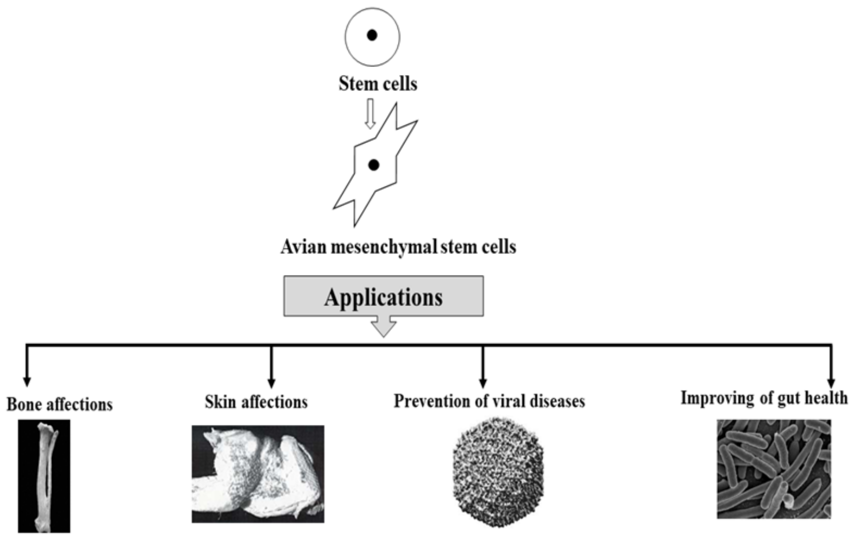

Figure 1 – The different applications of MSCs in the poultry field.

4.1. Bone affections

The calcium (Ca) level in blood is so important for increasing bone strength. Insufficient supply of dietary Ca can result in keel bone fracture (Toscano et al., 2020). Besides, vitamin D3 has relations to immunity, anti-oxidative and anticancer factors, cardiovascular functions, and bone development, such as differentiation and mineralization of osteogenic cells (Rath et al., 2000; Pande et al., 2015). Vitamin D3 facilitates Ca absorption. Thus, supplementation with adequate Ca and vitamin D3 in the diet is essential to avoid some bone disorders, such as tibial dyschondroplasia, especially in laying hens (Iqbal et al., 2018). MSCs have the capability for self-renewal and differentiation into osteogenic lineages. Therefore, they can be used during osteogenesis as a mineralization factor. The stimulatory effects of calcitriol [1, 25-(OH) 2 D3] on osteogenic differentiation and mineralization have been reported in humans (Li et al., 2012), rodents (Kim et al., 2016; Xiong et al., 2017), and chicken osteoblasts (Broess et al., 1995). The *in vitro* study of Pande et al. (2015) revealed that calcitriol could inhibit mineral deposition and decrease cell proliferation in chicken MSCs undergoing osteogenic differentiation.

4.2. Skin affections

Some skin affections, such as gangrenous dermatitis caused by *Clostridium perfringens*, *Clostridium septicum*, and *Staphylococcus aureus,* can induce adverse losses in the poultry production system (Li et al., 2010; Gornatti-Churria et al., 2018). Gangrenous dermatitis causes edema, congestion, hemorrhages, and necrosis of the skin of the breast, abdomen, back, thighs, tail, and wings of the broilers (Shivaprasad, 2016), resulting in low meat quality (Dinev et al., 2019)**.** Though gangrenous dermatitis is an affection of the skin, it has been regarded as a tissue-related and immune-mediated disease. In the study of Sohail et al. (2012), the findings revealed that broiler chickens with gangrenous dermatitis showed increasing levels of T cells, B cells, macrophages, interleukin (IL)-8, interferon (IFN) α, and nitrous oxide, but decreasing the proliferation of splenocyte in response to concanavalin A or lipopolysaccharide. Because MSCs can modulate the immune systems, they could be considered a good tool for the alleviation of tissue-related diseases caused by the previously mentioned bacteria (Golchin et al., 2019).

4.3. Prevention of IBDV

One of the most important immunosuppressive disease viruses of young chickens is IDBV (Dey et al., 2019). It has been detected in the immune organs, such as the bursa of Fabricius and the bone marrow of the affected chickens (Kabell et al., 2005). MSCs can express cell adhesion molecules for cell interactions for the release of cytokines and growth factors, which are essential for hematopoietic cell differentiation (Tippenhauer et al., 2013). These cytokines include IFN α and IFNγ (Liu et al., 2010), as well as IL-2, IL-6, and IL-18 (Rautenschlein et al., 2002; Ruby et al., 2006). It is known that IBDV cannot multiply in chicken fibroblast cells (Heo et al., 2011), so MSCs could be a target for IBDV infection. As a result of the fact that MSCs can help in proliferation and differentiation of hematopoietic precursor cells differentiation and proliferation, maybe there is an interaction between IBDV and MSCs (Majumdar et al., 1998). Therefore, MSCs could be a promising strategy for the production of vaccines against IBDV.

4.4. Improving gut health

It has been reported that MSCs may interact with a large number of intestinal bacteria that induce important effects on the functions of MSCs (Carrade and Borjesson, 2013; Lotfinegad, 2014). During intestinal inflammation, MSCs are capable of engrafting in the lamina propria of the gut and inducing potential immuno-regulatory functions (Zimmermann et al., 2012). This phenomenon is very important for analyzing the interactions between MSCs and the competitive exclusion compounds (probiotics and prebiotics), which helps in the replacement of the antibiotic growth promotor's applications.

5. Conclusion

Very little is known about the pathogenesis of avian MSCs. Besides, few studies showed the beneficial effects of avian MSCs. Therefore, research on the properties of avian multipotent stem cells is needed, which will lead to renewed interest in their extended applications in the poultry field.

Conflict of interest: The author declares no conflict of interest.

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