CHAPTER 1

INTRODUCTION

1. Introduction

Mesenchymal stem cells (MSCs) are defined as an adult immature cells, capable of self-renewing and of differentiating into various tissues *in vivo* and *in vitro* (Bianco *et al.,* 2001). Systemic administration of autologous or allogeneic MSCs in healthy animals has been reported to lead to the migration and engraftment of them in nonhematopoietic tissues (Devine *et al.,* 2003), whereas in injury models, they migrate specifically to the site of damage and undergo tissue-specific differentiation patterns (Chapel *et al.,* 2003; Barry *et al.,* 2004). Expression of a variety of adhesion molecules on MSCs may account for their potential multi-organ homing capacity (Zhao *et al.,* 2004). The multilineage differentiation ability, together with their extensive capacity for plastic expansion, led to important approaches of utilizing MSCs for tissue engineering as well as for gene therapy for a variety of congenital and acquired diseases (Barry *et al.,* 2004). Clinical trials involving MSCs concern distinct disorders, such as facilitation of hematopoietic recovery in hematopoietic stem cell transplantation (Koc *et al.,* 2000), osteogenesis imperfecta (Horwitz et al., 1999), metabolic diseases (Koc *et al.,* 2002), and myocardial infarction (Chen *et al.,* 2004)

MSCs are not inherently immunogenic, being unable to be recognized by allogeneic T-cells or natural killer cells (Rasmusson *et al.,* 2003). They express negligible levels of major histocompatibility complex (MHC) class II and intermediate levels of MHC class I molecules (Le Blanc *et al.,* 2003). Induction of MHC class II on MSCs by interferon-γ (IFN-γ) does not stimulate alloreactivity (Le Blanc *et al.,* 2003). Moreover, MSCs seem to be natural immunosuppressive elements, being able to inhibit *in vitro* T cell proliferation and function of both naive and memory T cells (Di Nicola *et al.,* 2002) or to suppress the development of monocyte-derived dendritic cells in an *in vitro* system (Zhang *et al.,* 2004).

The ability of MSCs to modulate immune responses implies their potential role in cellular immunoregulatory therapy by facilitating engraftment in organ transplantation (Bartholomew *et al.,* 2002) and re-introducing tolerance in

autoimmune diseases (Ikehara *et al.,* 2003). To this end, MSCs have already been used in a clinical trial for the effective treatment of acute graft versus host disease (Le Blanc *et al.,* 2004).

These characteristics make MSCs very promising candidates to develop new cell-based therapeutic strategies, such as the treatment of mesenchymal tissue injuries or supportive application in the context of hematopoietic stem cell (HSC) transplantation (Koc *et al.,* 2000; Horwitz *et al.,* 1999). Although bone marrow (BM) has been the main source for the isolation of multipotent MSCs, the harvest of BM is a highly invasive procedure and the number, differentiation potential, and maximal life span of MSCs from BM decline with increasing age (Koc *et al.,* 2000; Stenderup *et al.,* 2003). Therefore, the search for alternative source of MSCs for autologous and allogenic is of significant value. It has been reported that MSCs could be isolated from various tissues, including adipose tissue (Rodeheffen *et al*., 2008), umbilical cord blood (De *et al*., 2003; Ichim *et al*., 2008), umbilical cord tissue (Lu *et al*., 2006), Wharton's jelly (Mitchell *et al*., 2003), placenta (Miao *et al*., 2006) and amnion (Alviano *et al*., 2007). Among those, postnatal tissue including umbilical cord, Wharton's jelly, placenta and amnion are accessibility, painless procedures to donors, promising sources for autologous cell therapy and lower risk of viral contamination (Lu *et al*., 2006). As BM-MSCs are best characterized, we asked whether MSCs derived from other sources share the characteristics of BM-MSCs.

Therefore, the first goal of the present study was to verify whether cells with MSCs traits can be isolated from postnatal tissues including umbilical cord, Wharton's jelly, placenta and amnion under identical *in vitro* conditions with BM-MSCs. Second, those cells were to be compared to BM-MSCs, with respect to their morphology, immunophenotype and expansion potential. In addition, immunosuppressive properties of those cells were also determined. The results obtained from this study might be provided the novel sources of MSCs for future cell-base therapeutic applications.

2. Objectives

2.1 Overall objective

The overall objective of this study was to isolate and investigate MSCs from umbilical cord, Wharton's jelly, placenta and amnion in comparison to bone marrow-derived MSCs.

2.2 Specific objectives

To address the overall objective, 3 specific objectives were defined.

1.To isolate MSCs from umbilical cord, Wharton's jelly, placenta, amnion as well as bone marrow.

2.To characterize MSCs-derived from umbilical cord, Wharton's jelly, placenta and amnion in comparison to bone marrow derived MSCs in term of morphology, immunophenotype, expansion potential and multilineage differentiation capacity.

3.To study the immunosuppressive potential of MSCs-derived from umbilical cord, Wharton's jelly, placenta and amnion in comparison to bone marrow derived MSCs.