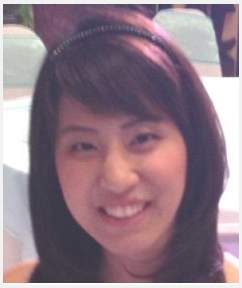
ImmunoTools *special* Award 2015



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Establishment of an in vitro model for characterizing immunotoxicology in humans by using umbilical cord-derived mesenchymal stem cells

Developmental immunotoxicity (DIT) refers to an early-life exposure to environmental risk factors, which induced disruption of normal immune system development. DIT may elicit either immunosuppression or immunostimulation resulting in adverse health outcomes (1). Animal studies, mostly in rodents, revealed that early-life exposure with certain drugs (e.g. diethylstilbestrol), heavy metals (e.g. lead), aflatoxin B1, and/or polycyclic aromatic hydrocarbons altered immune function (2). Furthermore, recent human data emphasized the link between DIT and the risk of non-communicable diseases. For instances, children exposed to air pollutions (e.g. polycyclic aromatic hydrocarbons, particular matter, and environmental tobacco smoke) had immune dysregulations with the increased risk of childhood asthma (3, 4). Numerous studies also indicated that *in utero* arsenic exposure increases susceptibility to respiratory infections among infants in both cohorts from Bangladesh (5) and United States (6), as well as prevalence of inflammatory diseases such as cardiovascular diseases in Bangladesh children (7). In addition, perinatal exposure to polychlorinated biphenyls was associated with increased incidence of respiratory infections (8) and reduced antibody response (8, 9), as well as increased the risk of allergic sensitization in their offspring (10). In view of the possible role of immune alterations in various increasing childhood diseases together with realization that the developing immune system is more sensitive than the adult immune system (11), there are significant advantages in extending immunotoxicity evaluations in ways that can directly screen prenatal immunotoxicants in humans. It is widely accepted that fetus is uniquely susceptible for xenobioteic exposure as a large variety of substances with diverse molecular structures are readily pass through placental barrier from mother to fetus (12).

Mesenchymal stem cells (MSCs) are non-hematopoietic stem cells that originally isolated from bone marrow, where they play a major role in regulation of hematopoiesis. MSCs have been currently identified in several tissues such as adipose tissue, dental pulp, umbilical cord, and umbilical cord blood. Although the physiological function of MSCs in those tissues remains unclear, MSCs have ability to differentiate into several types of cells under appropriate in vitro conditions, which could indicate tissue repair capacity (13). As a key regulator of hematopoiesis process, MSCs can produce a variety of growth factors, cytokines, chemokines, and proteases to support the survival, growth and differentiation of hematopoietic stem cells into all type of immune cells (14). Therefore, any damage to MSCs would seriously disrupt the homeostasis of immune system. In consideration of the fact that

MSCs derived from umbilical cord have the same immunomodulatory properties like bone marrow-derived MSCs and the process for collecting umbilical cord is not invasive as well as less painful than bone marrow aspiration, umbilical cord-derived MSCs hold great potential in DIT screening as they could reduce the number of animals used as well as the uncertainties due to interspecies extrapolations. This would provide a more rational basis for calculating dosages and setting human exposure limits. From a mechanistic standpoint, this in vitro model allows us to further elucidating the molecular mechanism(s) mediated by toxicants. In light of above, it is necessary to establish an in vitro model for characterizing immunotoxicology in humans by using umbilical cord-derived mesenchymal stem cells.

The ImmunoTools **Reagents Award** would be of great benefit to this project for performing the following objectives: 1) to identify MSCs, which is isolated from human umbilical cord, by immunophenotyping with the following fluorochrome-conjugated human antibodies: FITC-CD105, FITC-HLA-DR, PE-CD90, PE-CD34, PE-CD45, PE-CD19, PE-CD11b; 2) to investigate the effect of environmental toxicants on secretion of immunomodulatory cytokines by MSCs with following human ELISA kits: IFN-γ, IL-10, TNF-α, IL-4, and sCD147; and 3) to assess the hematopoietic supportive function of MSCs by using the following recombinant human proteins: IL-3, GM-CSF, and SCF.

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