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TOWARD PERSONALIZED CELL THERAPIES: HUMAN PLURIPOTENT STEM CELLS AS A RESEARCH AND THERAPEUTIC TOOL FOR LIVER DISEASES

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ABSTRACT

Regenerative medicine aims to revive and restore vital functions of the organs injured by pathological or iatrogenic factors. Due to the scarcity in organ donors and limited regenerative capacity of tissue-residing stem cells, *in vitro* generation of patient-specific therapeutic cells holds an immense promise for treating various degenerative diseases, cancers, genetic defects and toxicity induced-organ failures (1). While granting the potential of autologous multipotent stem cells as compatible transplantation cellular resources, which have had been explored extensively by many research teams globally, these cells possess some shortcomings owning to their limited growth, differentiation capacities. Moreover, lack of an ideal research cellular tool hampered the development of an efficient in vitro differentiation culture system. Pluripotent stem cells (PSCs) are able to replicate indefinitely *in vitro* (self-renewal) and can differentiate into cells of all three embryonic germ layers (pluripotent) that make up the adult organism. Owning to these characteristics, human PSCs are considered to be therapeutically valuable cellular resources.

We have showed that epigenetic reprogramming using epigenetic modifiers are able to confer pluripotent state in multipotent stem cells without genetic modifications (1) which offers a safer resource of induced pluripotent counterparts. Despite having derive and establish pluripotent stem cell, generation of therapeutically valuable cells such as hepatocyte is the key challenge. This has been hindered as the signalling pathways regulating the hepatic differentiation process and culture conditions that enhance the maturation and functionality of the tissue remains ambiguous. We have shown that by understanding the 2 key strategies [1] modulation of signalling pathways to explore molecular mechanisms controlling hepatic fate and differentiation; [2] developing a 3-dimensional (3D) culture system to improve the functionality of hESC-derived hepatocytes.

We have reported that the inhibition of PI3K signalling pathway indeed showed to improve the efficiency of AA-induced definitive endoderm (DE, prerequiste of hepatic differentiation) specification in chemically-defined culture condition, subsequently hepatic differentiation (3). We found that the suppression of PI3K/Akt signaling modulates both Nodal/Activin and β-catenin signalling pathways, the two most important signalling involved in DE cell fate specification. Meanwhile, the pluripotent stem cell-derived DE showed a superior maturation

and functionality in 3D culture microenvironment compared to the monolayer format (4). Collectively, these studies have demonstrated a significant cornerstone in the strategies to generate pluripotent stem cells to the transplantable standard and modulation of culture microenvironment using appropriate differentiation signal and 3D niche improve hepatic differentiation. Hence, these approaches will be a significant cornerstone in securing targeted and safer cell therapies tailored to suit the needs of patients and provides a good cellular model system for fundamental medical and pharmaceutical research.

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