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A Serum- And Feeder-Free Culture System for the Robust Generation of Human Stem Cell-Derived CD19+ B Cells and Antibody-Secreting Cells

Authors : Kirsten Wilson, Patrick M. Brauer, Sandra Babic, Diana Golubeva, Jessica Van Eyk, Tinya Wang, Avanti Karkhanis, Tim A. Le Fevre, Andy I. Kokaji, Allen C. Eaves, Sharon A. Louis, and Nooshin Tabatabaei-Zavareh

Abstract : Long-lived plasma cells are rare, non-proliferative B cells generated from antibody-secreting cells (ASCs) following an immune response to protect the host against pathogen re-exposure. Despite their therapeutic potential, the lack of in vitro protocols in the field makes it challenging to use B cells as a cellular therapeutic tool. As a result, there is a need to establish robust and reproducible methods for the generation of B cells. To address this, we have developed a culture system for generating B cells from hematopoietic stem and/or progenitor cells (HSPCs) derived from human umbilical cord blood (CB) or pluripotent stem cells (PSCs). HSPCs isolated from CB were cultured using the StemSpan™ B Cell Generation Kit and produced CD19+ B cells at a frequency of 23.2 ± 1.5% and 59.6 ± 2.3%, with a yield of 91 ± 11 and 196 ± 37 CD19+ cells per input CD34+ cell on culture days 28 and 35, respectively (n = 50 - 59). CD19+IgM+ cells were detected at a frequency of 31.2 ± 2.6% and were produced at a yield of 113 ± 26 cells per input CD34+ cell on culture day 35 (n = 50 - 59). The B cell receptor loci of CB-derived B cells were sequenced to confirm V(D)J gene rearrangement. ELISpot analysis revealed that ASCs were generated at a frequency of 570 ± 57 per 10,000 day 35 cells, with an average IgM+ ASC yield of 16 ± 2 cells per input CD34+ cell (n = 33 - 42). PSC-derived HSPCs were generated using the STEMdiff™ Hematopoietic - EB reagents and differentiated to CD10+CD19+ B cells with a frequency of 4 ± 0.8% after 28 days of culture (n = 37, 1 embryonic and 3 induced pluripotent stem cell lines tested). Subsequent culture of PSC-derived HSPCs increased CD19+ frequency and generated ASCs from 1 - 2 iPSC lines. This method is the first report of a serum- and feeder-free system for the generation of B cells from CB and PSCs, enabling further B lineage-specific research for potential future clinical applications.

Keywords : stem cells, B cells, immunology, hematopoiesis, PSC, differentiation
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