Journal club

STEM CELL RENEWAL THEORY TURNS 60

Following their seminal work in the early 1960s on bone marrow transplantation in irradiated mice, James Till and Ernest McCulloch have been rightly credited for defining the principles that underpin modern stem cell biology. However, for many, the foundations of the adult stem cell field were laid a decade earlier, in 1953, in a remarkable study by two other Canadians, Yves Clermont and Charles Philippe Leblond.

In mammals, the sequence of meiotic cell divisions that characterizes sperm production is the final stage of a long cellular hierarchy, involving multiple rounds of mitotic divisions of diploid germ cells, known as spermatogonia. Spermatogonia are classified into three types (A, intermediate and B) on morphological grounds. As they progress through the periodic seminiferous cycle, spermatogonia undergo rounds of cell division at defined stages. By analysing which cell types were present at each of these rounds of division, Clermont and Leblond identified their lineage hierarchy. By quantifying the cell number at each stage, the authors proposed that a minority of A-type spermatogonia — which they termed 'stem cells' — do not transform into intermediates, but instead enter a 'dormant' phase, ready to reactivate at the start of the next seminiferous cycle. Later, advances in phase-contrast microscopy revealed that spermatogonia are arranged in syncytial chains, suggesting that singly isolated cells (A_{single}) are the spermatogenic stem cells.

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Leblond's early studies were ground-breaking, as they were the first to emphasize that the maintenance of proliferating adult tissues could only be consistent with cell fate asymmetry (a defining property of stem cells), and that understanding cell fate behaviour demanded dynamic measures — the "time dimension in histology". This work on spermatogenesis and the 'stem cell renewal theory' anticipated much of the subsequent thinking on stem cell quiescence, fate asymmetry and equipotency. Indeed, long before the development of transgenic animal models, Leblond's pioneering and meticulous lineage tracing studies of epithelial maintenance in the intestine and oesophagus, using radioautography, were arguably the first to introduce the concepts of multipotency and stochasticity into the lexicon of adult stem cell biology.

It would be fitting if the sixtieth anniversary of the seminal paper by Clermont and Leblond would inspire readers to revisit Leblond's writings to discover more of his visionary thinking.

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