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Affinity-selection of heparan sulfate glycosaminoglycans: A promising strategy to augment stem cell therapy

Statement of the Problem: Bone marrow-derived mesenchymal stem cells (hMSCs) are a valuable resource for cell-based therapy. However, their abundance is low, necessitating ex vivo expansion to reach useful numbers; such expansion compromises their "stemness". Fibroblast Growth Factor-2 (FGF2), now in widespread use, increases hMSC proliferation, but triggers premature differentiation. Certain heparan sulfate (HS) glycosaminoglycan variants, abundant in stem cell Extracellular Matrix (ECM), are known to regulate the activity of many growth factors, including FGF2. Heparin has been used extensively to support human stem cell expansion as an analogue of the more physiologically relevant HS, although it adversely affects hMSCs, resulting in senescence. To obviate the need for heparin, we have isolated HS variants better targeted to the growth factor FGF2. An affinity chromatographic approach was utilized to extract an HS variant (HS8), using peptide sequences derived from the heparin-binding domains of FGF2 as bait. ELISA assays demonstrated that HS8 binds to FGF2 with much higher affinity than to other FGFs, as well as to other heparin-binding factors such as PDGF or VEGF. The melting temperature of FGF2 was markedly increased by HS8, indicating it acts to stabilize FGF2, so prolonging its activity. Both FGF2-stimulated ERK signaling and proliferation were amplified by HS8 in hMSCs. Crucially, hMSC cultures expanded with HS8 supplementation yielded a subpopulation of cells enriched for the early marker Stro-1+ as well as displaying greater CFU-F capacity. When applied into critical-sized calvarial defects in rats, HS8 significantly accelerated bone healing. Our work demonstrates that affinity-selection of HS is able to enrich for HS variants that can trigger faster hMSC ex vivo expansion without adversely changing their biological properties or potential. Such HS preparations are components for the scale-up technologies required to meet the expanding clinical need for adult stem cells.

Biography

Victor Nurcombe obtained his PhD in Developmental Neurobiology from the University of Sydney in 1984. He took both CJ Martin and Humboldt Fellowships to initiate his Postdoctoral training at the Max-Planck Institute for Biochemistry in Munich, and then worked in Oxford, Paris and New York, before returning to Australia in 1990 first to the Walter & Eliza Hall Institute and hence to the University of Melbourne in 1992 as a Senior Lecturer. In 1998, he became a Reader and Associate Professor at the University of Queensland as Head of Developmental Biology, before being headhunted to the IMCB in Singapore as a Principal Investigator in Stem Cell Biology in 2003. In 2008, he became Senior Principal Investigator within the IMB. He is also Adjunct Professor at the LKC School of Medicine, Imperial College London-NTU, Singapore, as well as the University of Lille in France.

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