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Standardized platelet releasate products for clinical applications in cell therapy: A mathematical approach and an innovative quality control test

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Background: Expanded mesenchymal stem cells (MSC) can be utilized for advanced cell therapy. Growth factors can be extracted from human platelet concentrates by physical or chemical methods. Standardized animal-free ancillary materials are required to obtain expanded MSC (Good Manufacturing Practice). Pooling single-donor products reduces variability, but the minimal pool size was never determined. A method predicting biological activity of additives is presently lacking: NMR spectroscopy and MALDI-TOF mass spectrometry provide widespread molecular characterization of biological samples.

Methods: Platelet-apheresis products were frozen and thawed to obtain platelet lysates (PL) or added with $CaCl_2$ to produce Supernatant-rich-in-growth-factors (SRGF). Growth rates of MSC cultured in media containing PL or SRGF were compared. Concentrations of n=10 growth factors were measured by ELISA in n=44 single-donor SRGF. Data matrix was analyzed by a novel algorithm simulating pools (n=500) of single-donor data with growing sample size (from n=2 to 20) and estimating coefficient of variation (CV). For validation we measured a) the CV of growth factor concentrations in n=10 pools manufactured according to algorithm results, b) growth rates of MSC expanded by separate SRGF batches. NMR and MALDI-TOF spectra composition of single-donor PL and SRGF were analyzed.

Results: SRGF promoted higher proliferation rate vs PL. Growth factor concentrations in single-donor SRGF showed high variability. In silico analysis suggested that pooling n=16 single-donor SRGF reduced CV below 20%: results were confirmed assessing CV of concentrations in real pools of n=16 single SRGF. Separate SRGF pools failed to differently affect MSC growth rate. NMR and MALDI-TOF spectroscopy demonstrated segregation between PL and SRGF products.

Discussion: Results suggest that SRGF performs better than PL to stimulate MSC duplication. Our validated algorithm demonstrated that pooling n=16 single-donor SRGF products ameliorates consistency of biological activity of SRGF batches. NMR and MALDI-TOF could predict quality of media additives for cell therapy products.

Recent Publications

1. Agostini F, Polesel J, Battiston M Lombardi E, Zanolin S et al. (2017) Standardization of platelet releasate products for clinical applications in cell therapy: a mathematical approach. J. Transl Med. 15(1):107. Doi: 10.1186/s12967-017-1210-z.
2. Bernardi M, Agostini F, Chieregato K, Amati E, Durante C (2017) The production method affects the efficacy of platelet derivatives to expand mesenchymal stromal cells *in vitro*. J Transl 15(1):90. Doi: 10.1186/s12967-017-1185-9.
3. Borghese C, Agostini F, Durante C, Colombatti A, Mazzucato M, Aldinucci D (2016) Clinical-grade quality platelet-rich plasma releasate (PRP-R/SRGF) from CaCl2 -activated platelet concentrates promoted expansion of mesenchymal stromal cells. Vox Sang. 111(2):197-205. Doi: 10.1111/vox.12405.

Biography

Francesco Agostini is a Senior Scientist (Biologist) at the Aviano National Cancer Center (Aviano; PN, Italy). He studied at the University of Trieste where he obtained his PhD in Molecular Biomedicine in 2010. He is involved in Translational Research focusing his interest on GMP-compliant methods to expand mesenchymal stem cell for targeted drug delivery in the oncology field.

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