Bergmayr et al. BMC Pharmacology and Toxicology 2012, 13(Suppl 1):A67
http://www.biomedcentral.com/2050-6511/13/S1/A67

BMC Pharmacology & Toxicology

MEETING ABSTRACT Open Access

Pharmacological stimulation of murine and human hematopoetic stem cells

Christian Bergmayr[1], Christian Balasz[1], Zarzar Kazemi[1], Filza Hussain[1], Thomas Bauer[2], Herbert Strobl[2], Peter Selzer[3], Wolfgang Strohmaier[4], Michael Freissmuth[1], Eva Zebedin-Brandl[1*]

From 18th Scientific Symposium of the Austrian Pharmacological Society (APHAR). Joint meeting with the Croatian, Serbian and Slovenian Pharmacological Societies.
Graz, Austria. 20-21 September 2012

Background

Hematopoietic stem cell (HSC) transplantation is a standard procedure in the treatment of hematological disorders and also applicable to support aggressive chemotherapy in cancer. In practice, the clinical outcome is often limited by inefficient bone marrow (BM) engraftment or by low numbers of available stem cells. It would therefore be desirable to enhance engraftment by pharmacological stimulation. HSC require several signals for successful migration into the bone marrow. One of these signals is provided by stimulation of $G\alpha_s$[1]. Pretreatment with prostaglandin (PG) E_2 enhances engraftment via activation of $G\alpha_s$-coupled EP_2 and EP_4 receptors [2]. Treprostinil is a stable analogue of prostacyclin/PGI_2, which acts via IP, EP_2 and EP_4 receptors and is approved for treatment of pulmonary hypertension. Here we tested the hypothesis that treprostinil stimulates stem cell engraftment.

Methods

Generation of murine bone marrow-derived HSCs: Undifferentiated HSC (lineage-negative, Lin– cells) were isolated from murine BM, separated by MACS (magnetic-assisted cell sorting) and characterized by fluorescence-activated cell sorting (FACS). BM transplantation: Lin– cells were pretreated *in vitro* in the absence and presence of 10 μM treprostinil alone or in combination with 30 μM FSK for 1 h at 37°C. The cellular threshold for successful transplantation was determined by titrating the number of HSCs required to allow for survival of lethally irradiated recipient mice. Engraftment and transplantation efficiency was determined by the analysis of white blood cell counts.

Results

Trepostinil triggered a concentration-dependent accumulation of cAMP in murine Lin– cells with an estimated EC_{50} in the range of 0.3 μM. A treprostini-induced cAMP accumulation was also observed in human HSCs, which were also shown to express the mRNA encoding IP, EP_2 and EP_4 receptors. Treprostinil enhanced engraftment of HSCs; this conclusion is based on the following observations: (i) mice injected with treprostinil-pretreated Lin– cells had significantly higher levels of circulating white blood cells as compared to those receiving vehicle-treated Lin– cells ($p < 0.05$, unpaired t-test); (ii) when pretreated and untreated Lin– cells were mixed to compete for BM reconstitution, the pretreatment with treprostinil increased transplantation efficiency 1.5–3-fold; (iii) *in vitro* pretreatment of HSCs with trepostinil reduced the minimum number of cells required to rescue a mouse; (iv) engraftment of HSCs was further enhanced when treprostinil was also administered after injection of the pretreated HSCs.

Conclusions

Treprostinil is suitable for improving haematopoetic stem cell transplantaion. The observations allow for designing a protocol to test the compound in a clinical trial.

Author details
[1]Institute of Pharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, 1090 Vienna, Austria. [2]Institute of Immunology, Medical University of Vienna, 1090 Vienna, Austria. [3]Department of Radiation Oncology, Medical University of Vienna, 1090 Vienna, Austria. [4]SciPharm SàRL, 6131 Junglinster, Luxembourg.

Published: 17 September 2012

* Correspondence: eva-maria.zebedin@meduniwien.ac.at
[1]Institute of Pharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, 1090 Vienna, Austria
Full list of author information is available at the end of the article

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doi:10.1186/2050-6511-13-S1-A67
Cite this article as: Bergmayr *et al.*: Pharmacological stimulation of murine and human hematopoetic stem cells. *BMC Pharmacology and Toxicology* 2012 **13**(Suppl 1):A67.