Cell Stem Cell
Previews

Mechanism Unknown: Prostaglandin E2 May Improve HSC Therapies

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A recent publication in *Nature* by North et al. (2007) has implicated the eicosanoid prostaglandin E2 in enhancement of hematopoietic stem cell function in zebrafish and in mice. This work may have practical therapeutic value, but much remains to be determined before this possibility is realized.

Hematopoiesis is a dynamic process, regulated in part by soluble molecules (Shaheen and Broxmeyer, 2007) and beginning at the level of a long-term repopulating (LTR), competitive (C), and self-renewing (SR) hematopoietic stem cell (HSC) (Broxmeyer et al., 2006; Kondo et al., 2003). Studies in the mid 1970s implicated the eicosanoid prostaglandin E (PGE) in modulation of hematopoiesis at the level of mature subsets of HSC (e.g., spleen colony-forming unit, CFU-S) (Feher and Gidali, 1974) with more extensive studies assessing effects of PGE1 and -2 on lineage-restricted hematopoietic progenitor cells (HPC) using in vitro colony-forming assays (Pelus et al., 1979; Lu et al., 1986). In the last 20 years, few new insights have evolved on hematopoietic effects mediated by PGE. North and colleagues have now revitalized this area by implicating PGE2 and its production in the modulation of homeostasis of vertebrate HSC (North et al., 2007). They came upon a role for PGE2 in LTR/C-HSC function through a screening process in which a panel of biologically active compounds was assessed for induction of stem cell expansion in zebrafish. Chemicals that enhanced synthesis of PGE2 increased HSC function; those that blocked PG synthesis decreased HSC function. Moreover, a stable derivative of PGE2, 16, 16-dimethyl (dm) PGE2, enhanced kidney marrow recovery in irradiation-induced injury in adult zebrafish. A similar capacity for PGE2 was observed in mammals, in that exposure of murine bone marrow to dm PGE2 increased the repopulation capacity of these cells in a transplant setting. Of note, dm PGE2 treatment of bone marrow cells elevated the function of HSCs without inducing a specific expansion of LTR/C-HSCs, despite this having been the basis for the original screen in the zebrafish system.

HSC transplantation is a critical component of certain treatment modalities to cure a wide range of malignant and nonmalignant blood disorders. However, numbers of donor HSCs are sometimes limiting, especially for transplantation of adults or higher-weight children when umbilical cord blood is the source of donor HSCs (Broxmeyer, 2006). Efforts to ex vivo expand human HSCs for therapy have not been successful (Broxmeyer, 2006). North et al. (2007) envision a scenario in which modulation of the PG pathway can enhance expansion of HSCs for therapeutic use (North et al., 2007). Whether or not PGE2, modified PGE2, or modulation of PG production will prove effective for expanding LTR/C/SR-HSC remains to be determined. The authors treated whole mouse bone marrow with dm PGE2 ex vivo for 2 hr prior to quantitating by in vivo analysis the number of day 12 CFU-S (a stem cell not considered to have LTR HSC activity) and frequency of LTR/C-HSC (North et al., 2007). This resulted in an approximately 3-fold increase in day 12 CFU-S and a 4- to 5-fold enhancement in HSC frequency at 6–12 weeks. It is remarkable that a significant elevation of HPC and HSC activity was achieved during only 2 hr of exposure to dm PGE2. It is unlikely that any expansion of HSC number occurred within the 2 hr of ex vivo treatment and before the cells were transplanted. How, then, was the impact on HSC function mediated, and what role was played in vivo versus in vitro? Was a direct effect on the HSC imparted by division or "priming," or through PGE2 effects mediated by accessory cells, or by an indirect effect on nonhematopoietic cells within the treated cell population, such as endothelial cells or their progenitors?

PGE2 has a number of effects on HPC. PGE2 has myelosuppressive effects on CFU-M/GM (Pelus et al., 1979) and can enhance colony formation by erythroid (BFU-E) progenitors, effects mediated by T cells (Lu et al., 1986). Proof of direct PGE2 actions on HSC will be difficult to attain but would have to entail functional studies on single purified HSC. An initial step in this direction was performed by North and colleagues, in that a purified population, enriched for HSC and HPC cells, also exhibited elevated CFU-S potential following in vitro exposure to dm PGE2. It is possible that the enhancing effects of PGE on day 12 CFU-S and HSC may result from PGE-induced modulation of HSC homing. The authors suggested that changes in homing efficiency were not involved (North et al., 2007). However, the authors used mixed populations of cells in their assay, and to obtain definite proof regarding the impact on homing will require the assessment of purified populations of cells.

Of note, the largest enhancement in HSC frequency was apparent 6 and 12 weeks posttransplantation, with

a less-dramatic elevation in HSC frequency observed at 24 weeks. This could be interpreted as dm PGE2 having a greater enhancing effect on shorter- versus longer-term repopulating HSCs. Such activity would still be important, as an enhancement of short-term function with at least maintenance of LTR cells would be of potential clinical value. Secondary transplant studies, in which marrow cells from primary repopulated mice are transplanted into secondary irradiated recipients, would help determine if PGE2 effects were on an SR population of HSC or perhaps if the process of SR was being influenced.

Ex vivo expansion for clinical use is usually done by incubation of cells in vitro for days. It is hard to predict what effects, if any, dm PGE2 would have on such ex vivo cultures of LTR/C/SR-HSC. Moreover, these effects may differ depending on the composition of cell types in culture. Appreciation of which of the four different PGE receptors mediate the above effects could shed light on PGE2 function at a cellular and intracellular level. However, in clinical transplantation, simpler is better. The ability of dm PGE2 to manifest its effect within 2 hr could have great clinical efficacy, regardless of the mechanism of action.

The work of North et al. (2007) should invigorate interest in PGE modulation of hematopoiesis. We look forward with anticipation to further studies of PGE effects on HSC and ESC. Such studies should take us closer to realizing the potential for PGE modulation of stem cells for clinical utility.

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