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Evolutionary Conservation of Human CD34$^+$ Cell Endothelial Differentiation in the Zebrafish Embryo

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Abstract:
Background. We tested the zebrafish embryo as a novel system to study human CD34$^+$ progenitor cells (hCD34$^+$) differentiation toward the endothelial and hematopoietic lineages.
Methods and Results. hCD34$^+$ were isolated from cord blood and subsequently labelled either with orange cell tracker™ dye or infected with a lentivirus expressing GFP. Labelled hCD34$^+$ (500-1000 cells) were injected into the sinus venosus of developing wt and Tg(*fli1*:EGFP) transgenic embryos prior to immune system development. Embryos transplanted with labelled hCD14$^-$ cells were used as controls.
Time-lapse confocal microscopy at early time points (2 hours) showed hCD34$^+$ circulation in developing vessels of the transgenic embryos and no vascular occlusions. Some hCD34$^+$ integrated into the vessel wall, after their early adhesion to vascular structures. One day after transplantation, hCD34$^+$ injection resulted in severe vascular defects, as increased diameter of dorsal artery (DA) and cardinal vein (CV) (DA=3.8±1.4um *vs.* 8.2±2.9um, $p<0.05$ n=11; CV=6.9±0.6um vs. 13±2.3um, $p<0.01$, in control and hCD34$^+$ injected embryos, respectively), altered branching with ectopic sprouts in the growing vasculature (61/72 embryos), and abnormal angiogenesis in the yolk region (14/17 embryos). Further, it was found evidence of hCD34$^+$ differentiation into mature endothelial hVWf - and hCD31 - positive cells.
To investigate hCD34$^+$ plasticity in the early events of vascular development, we performed hCD34$^+$ transplantation into the zebrafish blastula. hCD34$^+$ behaved as hemangioblast, homing to both the vascular and the hematopoietic compartments. Finally, embryos injected with the specific *Vegfc* morpholino RNA, that display a vascular phenotype, were rescued by hCD34$^+$ cells transplanted 2 hours later at blastula stage (29/32 embryos), suggesting that transplanted hCD34$^+$ show a potent angiogenic activity that affects the developing vasculature of the *Vegfc* depleted embryos.
Conclusions. Our *in vivo* study demonstrates the evolutionary conservation of hCD34$^+$

differentiation mechanisms in the zebrafish embryo, supported by hCD34^{+} participation to the zebrafish blood vessels formation, and by hCD34^{+} production of angiogenic factors acting on resident embryonic vascular cells.
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Author Disclosure Block: **O. Pozzoli**, None; **M. Lacovich**, None; **E. Siciliano**, None; **D. Avitabile**, None; **C. Loralamia**, None; **C. Gilardelli**, None; **E. Vigna**, None; **A. Biondi**, None; **M.C. Capogrossi**, None; **F. Cotelli**, None; **M. Pesce**, None.

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