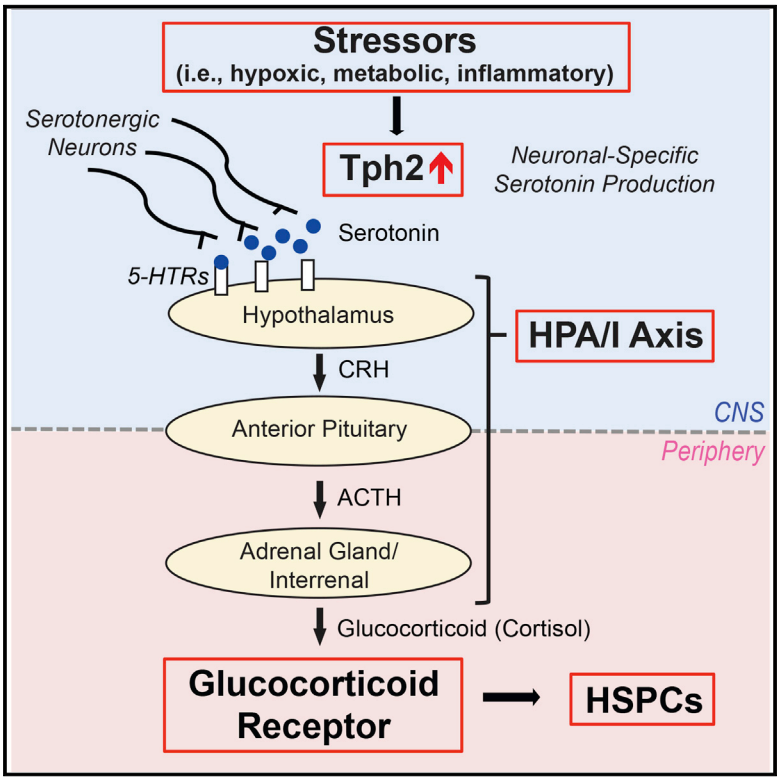
Article

Cell Stem Cell

The Central Nervous System Regulates Embryonic HSPC Production via Stress-Responsive Glucocorticoid Receptor Signaling

Graphical Abstract



Authors

Wanda Kwan, Mauricio Cortes, Isaura Frost, ..., Nadine Budrow, Wolfram Goessling, Trista E. North

Correspondence

tnorth@bidmc.harvard.edu

In Brief

In this study, North and colleagues uncover serotonin-stimulated central regulation of hematopoietic stem cell production during embryonic development, mediated by the stress-responsive hypothalamic-pituitary-adrenal/interrenal (HPA/I) axis and glucocorticoid receptor. Significantly, the hypoxic stress sensor Hif1α is a physiologic initiator of CNS-derived serotonin synthesis and central feedback regulation of embryonic HSC numbers.

Highlights

- Neuronal synthesis of serotonin is required for embryonic HSPC production in the VDA
- CNS-derived serotonin activates the HPA/I axis and GR to induce HSPC formation
- Direct exposure to GR agonists increases definitive HSPC numbers in the embryo
- The hypoxic stress sensor Hif1α initiates HPA/I-GR axis-mediated HSPC regulation

Kwan et al., 2016, Cell Stem Cell *19*, 370–382
September 1, 2016
http://dx.doi.org/10.1016/j.stem.2016.06.004

CellPress

Cell Stem Cell
Article

The Central Nervous System Regulates Embryonic HSPC Production via Stress-Responsive Glucocorticoid Receptor Signaling

Wanda Kwan,[1] Mauricio Cortes,[1] Isaura Frost,[1] Virginie Esain,[1] Lindsay N. Theodore,[1] Sarah Y. Liu,[1] Nadine Budrow,[1] Wolfram Goessling,[2,3] and Trista E. North[1,3,*]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02115, USA
[2]Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA
[3]Harvard Stem Cell Institute, Harvard University, Cambridge, MA 02138, USA
*Correspondence: tnorth@bidmc.harvard.edu
http://dx.doi.org/10.1016/j.stem.2016.06.004

SUMMARY

Hematopoietic stem and progenitor cell (HSPC) specification is regulated by numerous defined factors acting locally within the hemogenic niche; however, it is unclear whether production can adapt to fluctuating systemic needs. Here we show that the CNS controls embryonic HSPC numbers via the hypothalamic-pituitary-adrenal/interrenal (HPA/I) stress response axis. Exposure to serotonin or the reuptake inhibitor fluoxetine increased *runx1* expression and Flk1$^+$/cMyb$^+$ HSPCs independent of peripheral innervation. Inhibition of neuronal, but not peripheral, tryptophan hydroxlyase (Tph) persistently reduced HSPC number. Consistent with central HPA/I axis induction and glucocorticoid receptor (GR) activation, GR agonists enhanced, whereas *GR* loss diminished, HSPC formation. Significantly, developmental hypoxia, as indicated by Hif1α function, induced the HPA/I axis and cortisol production. Furthermore, Hif1α-stimulated HSPC enhancement was attenuated by neuronal *tph* or *GR* loss. Our data establish that embryonic HSC production responds to physiologic stress via CNS-derived serotonin synthesis and central feedback regulation to control HSC numbers.

INTRODUCTION

The formation and maintenance of hematopoietic stem and progenitor cells (HSPCs) is a complex process requiring coordination of signals from a variety of cellular inputs and a balance between self-renewal and differentiation. Definitive HSPCs first arise from the hemogenic endothelium in the ventral wall of the dorsal aorta (VDA), within the aorta-gonad-mesonephros (AGM) region, via an evolutionarily conserved process termed endothelial-to-hematopoietic transition (EHT) regulated by the transcription factor Runx1. A multitude of molecular and cellular interactions required locally for hemogenic niche specification have been identified (Carroll and North, 2014). Furthermore, HSPC emergence is exquisitely timed to match embryonic growth, with local developmental cues including metabolism, hypoxia, and shear stress acting to initiate EHT (Harris et al., 2013; Imanirad et al., 2014; North et al., 2009). However, in contrast to their initial specification, the mechanisms by which the embryo coordinates the rate of HSPC production and/or expansion to developmental needs (stressors), including continued growth and hematopoietic differentiation, are relatively uncharacterized.

On an organism-wide scale, stress response initiates in the brain. The CNS acts at the top of this hierarchy to sense stress signals and then communicates through neurotransmitters and neuronal circuitry to respond via neuroendocrine pathways to regulate responses in the periphery. Interestingly, several neuromodulators were identified in our prior in vivo zebrafish chemical screen for evolutionarily conserved HSC regulators (North et al., 2007). Adult human CD34$^+$ HSCs express select adrenergic, dopamine, serotonin, and gamma-aminobutyric acid (GABA) receptors (Spiegel et al., 2007; Steidl et al., 2004; Yang et al., 2007); however, the functional requirements of each are generally unclear. Catecholamines (noradrenaline [NA], adrenaline, and dopamine) can increase proliferation of CD34$^+$ human umbilical cord blood HSCs in vitro, promote HSC motility within the murine bone marrow (BM) niche, and enhance engraftment in immunodeficient mice (Spiegel et al., 2007). GABA likewise affects HSC migration (Zangiacomi et al., 2009), whereas serotonin can influence in vitro colony formation via direct hormonal stimulation (Yang et al., 2007). Recent studies showed that the sympathetic nervous system (SNS), which innervates peripheral tissues, responds to circadian signals to mobilize adult human and murine HSCs in the BM niche via catecholaminergic signaling (Méndez-Ferrer et al., 2008). Local SNS stimulation also affects embryonic HSPC development in the murine AGM (Fitch et al., 2012). These studies highlight the effects of local neuromodulation in the periphery on HSCs, particularly within the BM niche. However, it remains unclear whether this influence is only exerted in a locally restricted paracrine (hormonal) fashion, co-opted in ex vivo expansion protocols, or whether HSC production and homeostasis can be affected via distant neurotransmitter activity. In vivo utilization of central regulation during embryonic HSPC formation in response to developmental cues and/or stressors is likewise uncharacterized.

Serotonin (5-hydroxytryptamine, 5-HT), a biogenic amine that functions as neurotransmitter in the brain and hormone in the