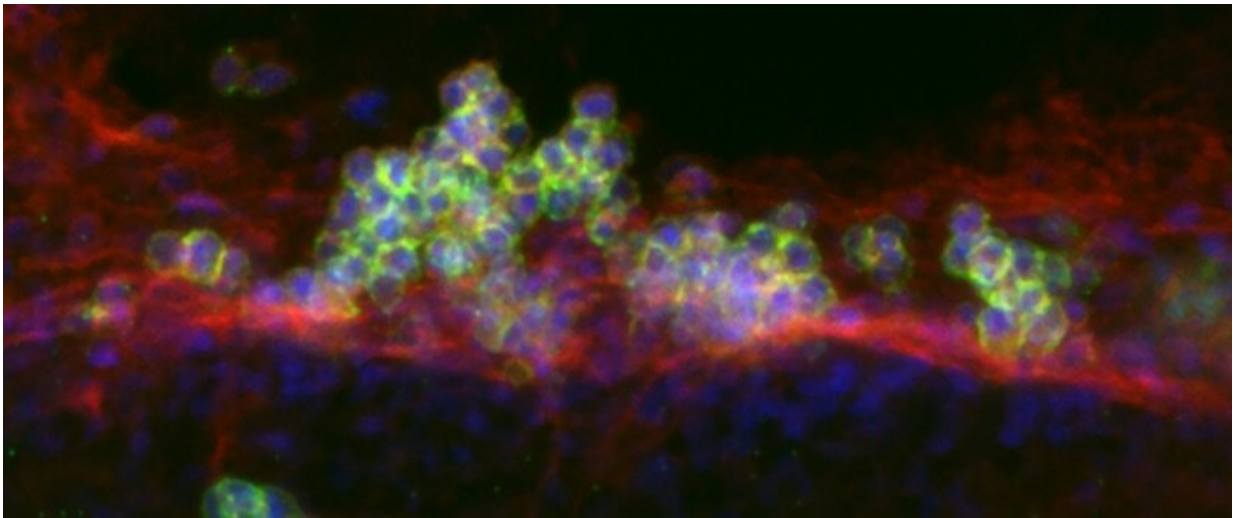


# Molecular landscape of the hematopoietic stem cell cradle

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A large cluster of hematopoietic stem cells and progenitor cells (green) attached to the wall of the aorta (red) of an embryo in which the *Svep1* gene was disabled. Credit: Laurent Yvernogeu, Hubrecht Institute

Researchers from the group of Catherine Robin at the Hubrecht Institute have characterized the molecular landscape of the aorta that supports the generation of the first hematopoietic stem cells (HSCs) in the embryo. HSCs are responsible for the constant replenishment of all blood cells throughout life. The researchers investigated which genes and regulatory pathways were active in the aorta of zebrafish, chicken, mouse and human embryos at the time of HSC formation. By comparing the

different species in vivo, they uncovered the complexity of the aortic microenvironment landscape and the fine-tuning of factors that interplay to control HSC generation both in time and space. Understanding the regulatory function of the local environment where HSCs are formed will pave the way for improved HSC production in vitro and clinical cell therapy for blood related diseases. The results are presented in the scientific journal *Blood*.

## **Hematopoietic stem cell need for the clinic**

The constant production of short-lived hematopoietic cells, or [blood cells](#), throughout life relies on a small number of hematopoietic stem cells (HSCs) present in the bone marrow in adults. Defective HSCs lead to blood-related disorders and cancers that are partly treated via HSC transplantations. For decades, efforts have been made to generate bona fide HSCs in vitro to circumvent the limited supply of donor compatible HSCs for [clinical use](#).

Despite recent progress, the culture protocols for HSCs in the lab remain sub-optimal in mimicking the physiological HSC surrounding microenvironment or niche. Such a niche is needed to induce the formation of HSCs and to preserve their stem cell properties for the long term (i.e., generation of all blood cell types with no exhaustion). A better knowledge of the regulatory factors and pathways involved in HSC formation in vivo is therefore required to improve in vitro culture protocols and HSC engineering (i.e., HSC generation, gene correction).

## **Exploring the aorta, the cradle of hematopoietic stem cells**

The defined location of a stem cell within a specific microenvironment regulates the fate, behavior and molecular identity of the stem cell via a

complex extrinsic regulation that is far from being fully elucidated. All HSCs derive from a specialized subset of endothelial cells, which form the blood vessels, named hemogenic endothelial cells through a process called endothelial-to-hematopoietic transition (EHT).

EHT occurs in the main arteries of the embryo, including the aorta, during early embryogenesis. After EHT, hematopoietic cells are organized in clusters transiently attached to the wall of the aorta, where cells progressively acquire their HSC properties. EHT is a well-conserved process occurring in all vertebrates at precise locations in the aorta and at defined time points of development. This spatio-temporal restriction clearly indicates the presence of specific molecular cues in the surroundings of the aorta that instruct the aortic hemogenic endothelial cells, drive EHT and therefore HSC formation. How the aortic niche regulates these essential processes in vivo is still poorly understood.

## **The molecular landscape of the aortic niche and beyond**

To explore the molecular characteristics and key components of the aortic microenvironment where HSC emergence is spatially restricted, the researchers performed genome-wide RNA tomography sequencing (tomo-seq) on zebrafish, chicken, mouse and human embryos. Using this technique, they determined which genes were active in each embryo section along the anterior to posterior and dorsal to ventral axes of the embryo.

They used the resulting transcriptional maps to specifically explore the genes and regulatory pathways active in the aortic microenvironment. By comparing the data between species and doing functional analyses, they uncovered the complexity of the aortic microenvironment landscape.

They found that a fine-tuning of various factors controls the generation of HSCs. While some of these factors were specific for certain species, others were common to all species. The anterior-posterior (head to tail) and dorsal-ventral (back to front) transcriptional maps generated in this study also provide a powerful and unprecedented resource for the scientific community.

The researchers indeed offer the possibility to perform broader analysis via an [interactive website](http://multi-species.embryos.tomoseq.genomes.nl) ([multi-species.embryos.tomoseq.genomes.nl](http://multi-species.embryos.tomoseq.genomes.nl)), such as (i) to compare with precision the expression pattern of any given gene of interest in any structure or microenvironment along the body axes of four embryo species, (ii) to identify molecular signals that are potentially involved in tissue patterning (e.g. induction signal from neural tube/somite, notochord/somite) or (iii) to identify new genes that follow an expression pattern similar to that of a known gene.

## **New conserved regulators of HSC generation in vivo**

HSC regulation by extrinsic signals is a complex process that occurs via direct cell-cell contact or long-range distribution of secreted molecules, acting directly or by inducing secondary signals. By combining the tomoseq data on the aortic microenvironment and previously published RNA-seq data on HSC cluster [cells](#), the researchers identified ADM and RAMP2 as an important conserved ligand-receptor couple involved in the production of HSCs in vivo. They also uncovered the secreted protein SVEP1 as the first extrinsic regulator of both cluster cellularity and cluster cell fate towards an HSC fate.

Overall, the current study emphasizes the complexity of the aortic microenvironment landscape at the time of HSC formation and provides insights on the finetuning of various factors that interact with each other to control HSC production both in time and space as it occurs in vivo.

**More information:** Laurent Yvernogeu et al, Multispecies RNA tomography reveals regulators of hematopoietic stem cell birth in the embryonic aorta, *Blood* (2020). [DOI: 10.1182/blood.2019004446](https://doi.org/10.1182/blood.2019004446)

Provided by Hubrecht Institute

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