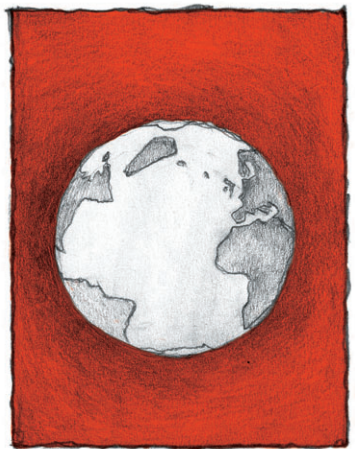
Keeping track of the literature isn't easy, so Outside JEB is a monthly feature that reports the most exciting developments in experimental biology. Short articles that have been selected and written by a team of active research scientists highlight the papers that JEB readers can't afford to miss.

Outside JEB

HYPOXIA TOLERANCE



LYMPHATICS ASSIST CIRCULATION DURING HYPOXIA

The vertebrate lymphatic system is a network of vessels that collects excess fluid from tissues, delivers the fluid to lymph nodes and then ultimately returns the fluid back to the circulatory system for redistribution. The system plays a critical role in the immune response, fluid balance and the transport of fatty acids. Moreover, the lymphatic system is guilty of transporting cancerous cells throughout the body, spreading cancer to new tissues. As such, many people are interested in studying the lymphatic system to better understand the development and treatment of cancer.

Recently, scientists have shown that lymphatic and circulatory vessels are connected in adults. However, the structure and function of these connections, called arterial-lymphatic conduits (ALCs), are unknown. Lasse Dahl Ejby Jensen from the Karolinska Institute in Stockholm, Sweden, together with colleagues from Sweden and Denmark examined ALCs in zebrafish and glass catfish and studied how hypoxia (low levels of oxygen) affects these connections since cancerous tissue is often hypoxic.

The research team used various microscopy techniques to examine the lymphatic system and the structure of the ALCs. Fortunately, zebrafish and glass catfish are completely transparent, so the authors also used video and photography to non-invasively observe the flow of blood and lymphatic fluid. They found that zebrafish and glass catfish have similar lymphatic systems and that ALCs often look like tangled corkscrew-shaped vessels, directly connecting lymphatic to arterial vessels.

Next, Jensen and colleagues compared fish exposed to hypoxia with those held in normal oxygen levels in order to better understand the functional relationship between the circulatory and lymphatic systems. Remarkably, the authors found that blood, containing red blood cells, flowed into the lymphatic vessels during hypoxia. This incredible finding suggests that the lymphatic system can act as a back-up for the circulatory system. This is a quick and easy way to ameliorate a hypoxic situation, with the lymphatic system stepping in to expand the circulatory system so that it does not have to grow new blood vessels and make new red blood cells.

The authors then wanted to figure out how blood enters the lymphatic system. Again using microscopy and video technology, they observed that during hypoxia, ALCs dilate and straighten, indicating that blood is entering the lymphatic system *via* the ALCs. Finally, Jensen and colleagues sought to determine which molecular players control this phenomenon. Nitric oxide (NO) is known to act on vascular smooth muscle cells to relax and dilate them. The authors used various chemicals to test whether NO induces the ALCs to relax during hypoxia and found that NO is indeed behind the hypoxia-induced flow of blood into the lymphatic system.

Jensen and colleagues have uncovered a new function for the lymphatic system: a back-up circulatory system in times of hypoxia. They demonstrated that ALCs act as gatekeepers for blood flow to the lymphatic system during hypoxia. These gates are controlled by NO, which causes ALCs to relax and straighten, allowing blood to enter. Findings from this study could be used to better understand how cancerous tumours, which can be hypoxic, could enter the lymphatic system from the circulation.

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Jensen, L. D. E., Cao, R., Hedlund, E.-M., Söll, I., Lundberg, J. O., Hauptmann, G., Steffensen, J. F. and Cao, Y. (2009). Nitric oxide permits hypoxia-induced lymphatic perfusion by controlling arterial-lymphatic conduits in zebrafish and glass catfish. *Proc. Natl. Acad. Sci. USA* **106,** 18408-18413.

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