

Stem cells used to model infant birth defect

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Hemangiomas -- strawberry-like birthmarks that commonly develop in early infancy - are generally harmless, but up to 10 percent cause tissue distortion or destruction and sometimes obstruction of vision or breathing. Since the 1960s, problematic hemangiomas have been treated with corticosteroids such as dexamethasone or prednisone. But steroids have considerable side effects, don't always work, and their mechanism of action in hemangioma has remained a mystery. Researchers at Children's Hospital Boston recently discovered that infantile hemangiomas originate from stem cells, and have used these stem cells to better understand this tumor in the laboratory.

In the March 18 issue of the [New England Journal of Medicine](#), they show that steroids target hemangioma stem cells specifically, reveal their mechanism of their action and suggest other possible ways to halt and shrink hemangiomas.

Hemangiomas, affecting 4 to 10 percent of infants, are noncancerous tumors consisting of a tangled mass of blood vessels. Previously, it was assumed that steroids act on endothelial cells, which make up about 30 percent of cells in the tumor. The new research, led by dermatologist Shoshana Greenberger, MD, PhD, working in the lab of Joyce Bischoff, PhD, in Children's Vascular Biology Program, shows that steroids interfere with a much rarer and more primitive cell type - hemangioma stem cells.

Greenberger and Bischoff further showed that steroids work by inhibiting hemangioma stem cells' ability to stimulate [blood vessel](#)

[growth](#), and that they do so by shutting down production of a specific factor called vascular endothelial growth factor (VEGF-A). VEGF is well known as a stimulator of angiogenesis (blood vessel growth) in cancer and age-related macular degeneration.

"We now have more therapies targeting VEGF, so our findings open the way to finding a more specific and safer therapy for hemangioma," says Greenberger.

Steroids usually result only in stabilization of hemangioma growth, and about 30 percent of hemangiomas don't respond to steroid treatment. Steroids also have side effects including facial swelling, hyperactivity, growth retardation and increased blood pressure. Although the effects on appearance may seem minor, research indicates that a baby's physical appearance can interfere with maternal bonding.

"My dream has always been to give a drug to stop hemangioma at its first appearance," says Children's plastic surgeon John Mulliken, MD, co-director of Children's Vascular Anomalies Center and a co-author on the study.

Greenberger, Bischoff and colleagues worked with hemangioma stem cells isolated from patient tissue samples provided by Mulliken, and showed that:

- When human hemangioma stem cells were pretreated with dexamethasone, then implanted in mice, the tumors that formed had far fewer blood vessels.
- Dexamethasone suppressed the stem cells' production of VEGF-A, but did not suppress VEGF-A production by [endothelial cells](#) from the same hemangioma.

- When VEGF-A production was suppressed in hemangioma stem cells using shRNA silencing, then implanted in the mice, there was an 89 percent reduction in vessel growth.
- VEGF-A was detected in actively growing hemangiomas, but not in regressing (involuting) hemangiomas.

Earlier research in Bischoff's lab and that of Bjorn Olsen, MD, PhD, of the Harvard School of Dental Medicine, indicates that hemangiomas may result from an in utero mutation in a stem cell destined to become an endothelial cell, causing a disruption in the normally well-ordered process of blood vessel development. Under a 2008 Translational Research Program grant from Children's, Bischoff's lab has been using hemangioma stem cells to test a library of existing medications that might specifically inhibit the proliferation of the hemangioma [stem cells](#), and thereby limit growth of the hemangioma tumor.

"Steroids are inhibiting expression of a central regulator of blood vessel growth: VEGF-A," says Bischoff. "But we'd like to target the stem cell itself - stop its proliferation, prevent it from differentiating into unwanted [blood vessels](#) and, at the same time, eliminate the cellular source of VEGF-A."

More information: Citation: Greenberger S, Boscolo E, Adini I, Mulliken J and Bischoff J. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. *N Engl J Med* 2010 Mar 18; 362(11):30-38.

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