Gene determines acceptance, rejection of stem cells from others of the same marine species

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Researchers studying a marine organism called Botryllus schlosseri have discovered a single gene that determines whether cells are accepted as self or destroyed by immune cells as non-self. Credit: Chris Patton

(Phys.org) —To live together harmoniously in our bodies, cells need to be able to distinguish which of those among them are sanctioned residents and which are interlopers. This way, native cells can be left alone to do their jobs, and foreign cells can be attacked and removed.

The ability to identify friend from foe is made possible by the major histocompatibility genes, or MHC genes, which in humans and other

vertebrates determine, for example, that a pregnancy is OK but organ transplants must be rejected (thus the need for immunosuppressants).

Now, researchers studying a marine organism called Botryllus schlosseri at Stanford's Institute for Stem Cell Biology and Regenerative Medicine and Stanford's Hopkins Marine Station have discovered a single gene that determines whether cells are accepted as self or destroyed by immune cells as non-self. Most important, the gene determines whether circulating germ-line stem cells (which can make sperm or eggs) from one Botryllus organism can invade and implant themselves in a related Botryllus organism.

The discovery, published July 26 in *Science*, reveals a gene and its many variants (alleles) that are unique and not directly related to the human MHC genes. However, the discovery of very primitive self-recognition gene variants should enhance our understanding of the evolution of the immune system, the scientists say. Publication of the gene sequences will allow researchers to explore how MHC genes work and to look for related human genes that might be involved in self/non-self recognition.

Botryllus schlosseri is an unusual marine organism, an invertebrate that is evolutionarily one of the closest living relatives of vertebrates. The researchers established this relationship in another study of the organism's entire genome sequence. (That study was published July 2 in *eLife*.)

The larval-stage Botryllus, which has a primitive brain and ventral neural chord (like a proto spinal cord), undergoes a metamorphosis to become an invertebrate. On a weekly basis, the invertebrate form of Botryllus reproduces by budding off new organisms. The individuals live together in a colony surrounded by a membrane or "tunic," fusing with one another other to form a shared circulatory system that moves fluid through the whole colony.

However, when two or more adjacent colonies touch, a recognition event occurs. Those colonies that share one or both alleles of the compatibility gene, called Botryllus histocompatiblity factor, fuse vessels and share blood-borne cells, while those that don't share a BHF gene have an inflammatory rejection that results in the formation of a scar between the colonies.

When the colonies share a common BHF-gene variant and form a common circulatory system, stem cells from one colony will travel to the other related colony and take up residence. The transplanted stem cells from one Botryllus colony can even take over the developing gonads of the other colony, turning what was once an individual into an incubator for its relatives' germ cells, said senior research scientist Ayelet Voskoboynik, PhD, a co-lead author of the paper.

To analyze the recently completed Botryllus genome for the histocompatibility gene, the authors developed and applied sophisticated new algorithms for genetic analysis. These tools automatically eliminate thousands of unlikely gene candidates and zero in on the needle in the haystack: the BHF gene itself, said postdoctoral scholar Aaron Newman, PhD, another co-lead author.

"This finding reveals a fusion-rejection system that is now understood to the point where one can reliably predict, based on BHF sequences, whether the colonies will reject or fuse with each other," said Irving Weissman, MD, professor of pathology and a co-senior author of the paper. "The fact that this system is totally unrelated to human major histocompatibility genes and the immune cells that mediate human tissue transplant rejection opens the door to a deeper understanding of the system's evolution and functions."

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