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Biologists Discover Solution to Problem Limiting Development of Human Stem Cell Therapies

Biologists at UC San Diego have discovered an effective strategy that could prevent the human immune system from rejecting the grafts derived from human embryonic stem cells, a major problem now limiting the development of human stem cell therapies. Their discovery may also provide scientists with a better understanding of how tumors evade the human immune system when they spread throughout the body.

The biologists developed "humanized" laboratory mice that contained a functional human immune system. Credit: Zhili Rong, UC San Diego

The achievement, published in a paper in this week's early online edition of the journal *Cell Stem Cell* by a collaboration that included scientists from China, was enabled by the development of "humanized" laboratory mice that contained a functional human immune system capable of mounting a vigorous immune rejection of foreign cells derived from human embryonic stem cells.

Because human embryonic stem cells are different from our own body's cells, or "allogenic," a normally functioning human immune system will attack these foreign cells. One way to reduce the body's "allogenic immune response" is to suppress the immune system with immunosuppressant drugs.

"For organ transplantation to save patients with terminal diseases that has been quite successful," says Yang Xu, a professor of biology who headed the team of researchers that included Ananda Goldrath, an associate biology professor at UC San Diego. "But for stem cell therapies, the long term use of toxic immunosuppressant drugs for patients who are being treated for chronic diseases like Parkinson's disease or diabetes pose serious health problems."

Researchers had long been searching for a human immunity relevant model that would allow them to develop strategies to implant allogenic cells derived from embryonic stem cells safely. “The problem is that we only had data from mouse immune system and those are not usually translatable in humans, because human and mouse immune systems are quite different,” explains Xu. “So what we decided to do was to optimize the humanized mouse that carries a functional human immune system.”

To do that, the biologists took immune deficient laboratory mice and grafted into their bodies human fetal thymus tissues and hematopoietic stem cells derived from fetal liver of the same human donor. “That reconstituted in these mice a normally functioning human immune system that effectively rejects cells derived human embryonic stem cells,” says Xu. With these “humanized” mouse models, the biologists then tested a variety of immune suppressing molecules alone or in combination and discovered one combination that worked perfectly to protect cells derived from human embryonic stem cells from immune rejection.

That combination was CTLA4-Ig, an FDA-approved drug for treating rheumatoid arthritis that suppresses T-cells responsible for immune rejection, and a protein called PD-L1 known to be important for inducing immune tolerance in tumors. The researchers discovered that the combination of these two molecules allowed the allogeneic cells to survive in humanized mice without triggering an immune rejection.

“If we express both molecules in cells derived from human embryonic cells, we can protect these cells from the allogenic immune rejection,” says Xu. “If you have only one such molecule expressed, there is absolutely no impact. We still don’t know exactly how these pathways work together to suppress immune rejection, but now we’ve got an ideal system to study this.”

He and his team of researchers also believe their discovery and the development of their humanized mouse models may offer the much needed tools to develop ways to activate immune response to tumors, because these molecules are known to be important in allowing tumors to evade the human immune system.

“You’re dealing with the same exact pathways that protect tumors from our immune system,” says Xu. “If we can develop strategies to disrupt or silence these pathways in tumors, we might be able to activate immunity to tumors. The humanized mouse system is really a powerful model with which to study human tumor immunity.”

Other researchers involved in the study, besides Xu and Goldrath, were Zhili Rong, Meiyan Wang, Martin Stradner and Huijuan Kong of UC San Diego; Zheng Hu, Huanfa Yi and Yong-Guang Yang of China’s Jilin University; Shengyun Zhu and Xuemei Fu of Shenzhen Children’s

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