Nerve healing: Neighboring cells become a police force and could make tumors benign

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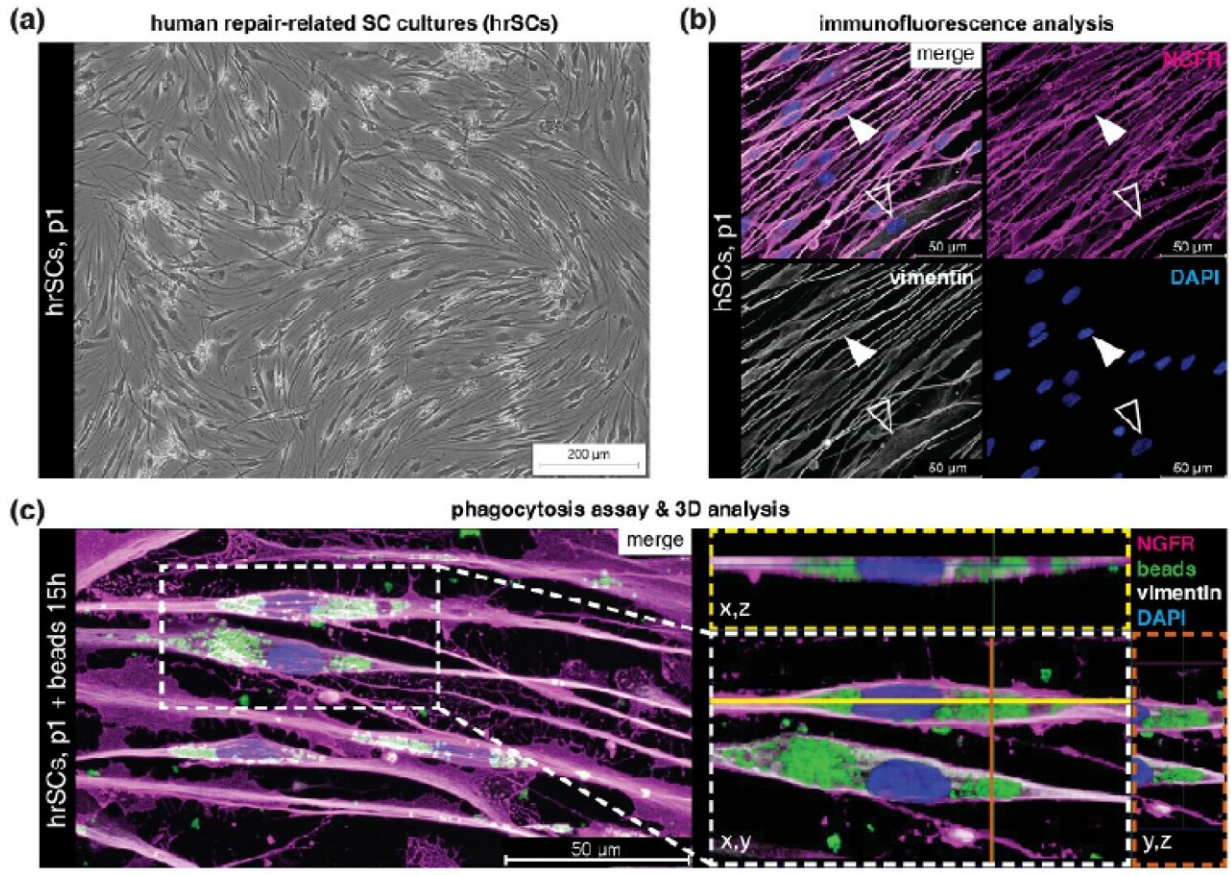

Phagocytosis potential and inflammatory response of hrSCs. (a) Phase contrast image of a representative passage 1 (p1) hrSC culture. (b) Immunostaining of p1 hrSCs for SC marker NGFR (magenta), intermediate filament vimentin (gray) and nuclear stain DAPI (blue); arrowheads indicate a NGFR negative and vimentin positive fibroblast. (c) 3D confocal image analysis of hrSCs exposed to 1 µm in diameter green fluorescent latex beads for 15 h. Cross sections show internalized beads within the SC cytoplasm. Credit: *Glia* (2022). DOI:

10.1002/glia.24257

Schwann cells are known to protect and repair nerve cells. Until now, however, it was not known that they themselves take over functions of certain immune cells during nerve healing. For example, they produce signaling molecules that can activate other immune cells. In particular, however, they are able to stop inflammatory reactions in order to prevent excessive tissue damage and allow the nerve to regenerate.

"This is essential, because inflammation releases free radicals against which nerve fibers cannot protect themselves. Therefore, the inflammation must be cleared quickly, which is precisely what Schwann cells do," explains Dr. Sabine Taschner-Mandl, who designed the study and heads a research group at St. Anna CCRI. The new results, in which the Medical University of Vienna is also significantly involved, were published in the journal *Glia*.

Do Schwann cells protect against malignancy?

How are these results related to tumor growth? After nerve injury, Schwann cells adopt a "repair" mode that is also found in benign infantile nerve tumors. There, it causes the tumor cells to mature and thus reach a stage where they lose their aggressive properties and no longer divide unchecked.

"Based on the current results, we now suspect that the immune cell functions of Schwann cells also become effective in childhood nerve tumors. This is because in cancer, there is always a kind of inflammation bubbling away that never comes to a halt. In benign nerve tumors, ganglioneuromas, the accompanying chronic inflammation could be stopped by Schwann cells similar to nerve healing, because unlike

malignancies, benign nerve tumors have many Schwann cells in their microenvironment. We also see that a lot of immune cells migrate into these tumors, for which the Schwann cells could also be responsible," says Sabine Taschner-Mandl.

Healthy Inflammation: First Activate, Then Shut Down

In particular, the current study shows that Schwann cells can influence certain immune cells, so-called T cells, which play an important role in the defense against cancer. Schwann cells—both those in nerve regeneration and those in benign tumors—carry MHC-I and MHC-II molecules on their surface that are important for T-cell regulation. Via these molecules, Schwann cells present recognition features of material they have previously taken up from their environment.

"We mimicked an inflammatory response in the laboratory and detected a whole range of additional stimulatory and inhibitory surface molecules that are also necessary for T cell activation," explains Jakob Berner, MSc, co-first author of the study and interim Ph.D. student in Kaan Boztug's group at St. Anna CCRI. "Our experiments show that Schwann cells are able to take up large amounts of material via phagocytosis."

As the first immune response to a nerve cut, Schwann cells secrete substances that attract T cells, macrophages and other immune cells. Now it turned out that not only a reaction between the classical immune cells takes place, but also between Schwann cells and T cells.

While Schwann cells initially fuel the inflammatory response by releasing interferon-gamma, they can later shut it down by up-regulating the T-cell inhibitory PD-L1 molecule.

"First activate, then shut down—that's the normal process of an

inflammatory response. If this were also the case in cancer, then it could curb cancer growth," comments Sabine Taschner-Mandl. Whether and how these findings can be used for potential cancer therapies is now being researched.

More information: Jakob Berner et al, Human repair-related Schwann cells adopt functions of antigen-presenting cells in vitro, *Glia* (2022). DOI: 10.1002/glia.24257

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