A new ally in fighting brain diseases: Your very own skull

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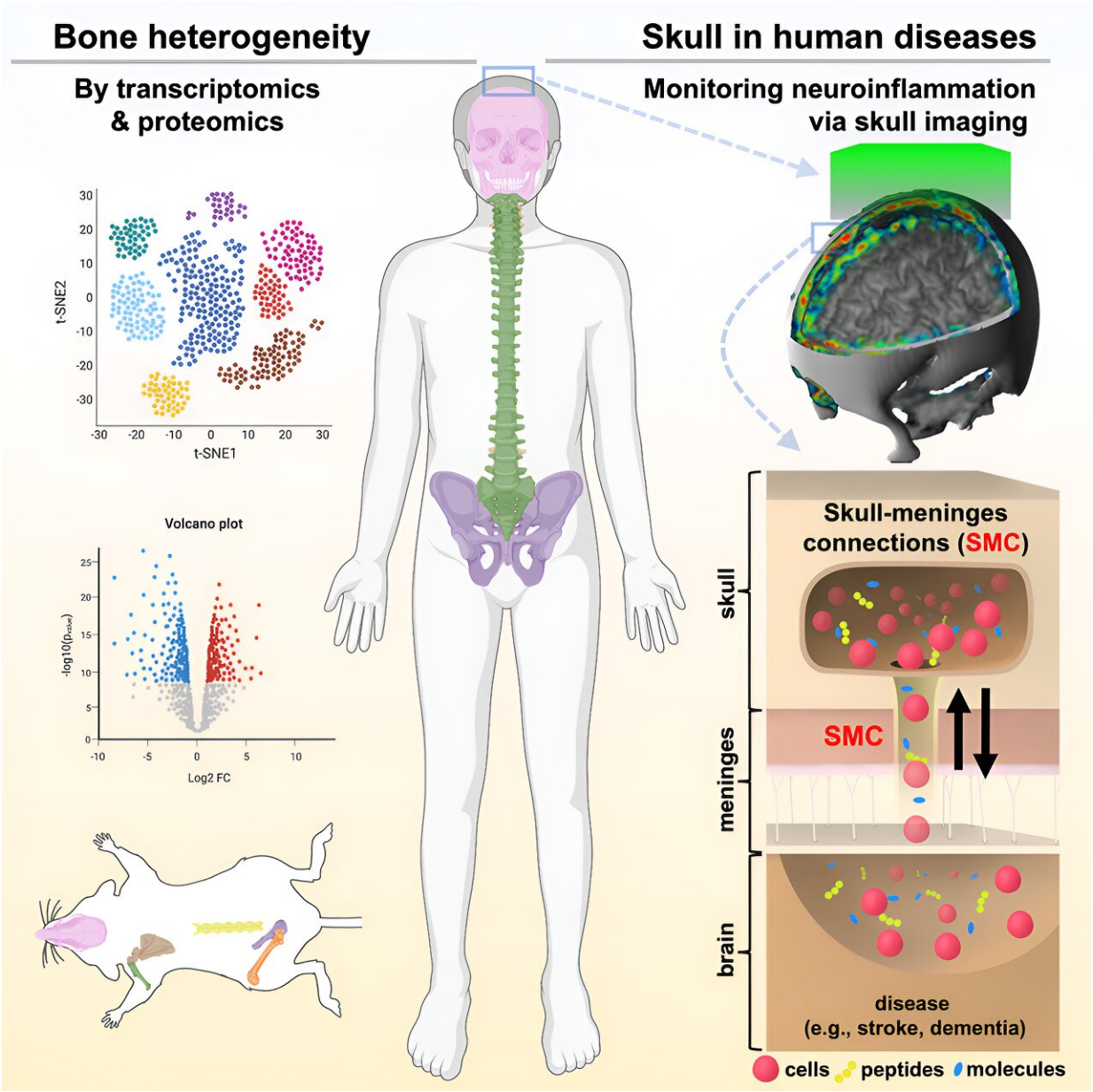

Graphical abstract. Credit: *Cell* (2023). DOI: 10.1016/j.cell.2023.07.009

Alzheimer's, stroke, multiple sclerosis and other neurological diseases cause severe damage due to neuroinflammation mediated by immune cells. Managing this inflammation poses a significant medical challenge because the brain is protected by the skull and additional surrounding membranes that make the brain less accessible for treatment approaches.

Scientists had previously discovered pathways going from the bone marrow of the skull towards the brain, allowing immune cell movement. Now, new research revealed that cells in the skull's bone marrow are unique in their composition and in their disease response. These findings offer new possibilities for the diagnosis and treatment of neurological diseases and revolutionize brain health monitoring in the future with non-invasive skull imaging. The results are now published in *Cell*.

Neurological diseases such as Alzheimer's, stroke, and multiple sclerosis have a devastating impact on the lives of millions worldwide. A common feature is neuroinflammation, an internal "fire" in the brain that can cause severe damage by activation of immune cells and release of inflammatory molecules.

However, due to the brain's relative inaccessibility, as it is shielded by the skull and three additional layers of protection in the form of membranes, controlling and monitoring this inflammation has been a major challenge. A team of scientists around Prof. Ali Ertürk at Helmholtz Munich in collaboration with researchers from the Ludwig-Maximilians-Universität München (LMU) and the Technical University of Munich (TUM) sought to address this unmet need.

Not just a helmet: The intricate connection between

the skull and brain

Defying traditional understanding that the skull and the brain have no direct interchange, recent studies have unveiled direct connections between the skull's bone marrow and the brain's outermost surface of the protective membranes, the meningeal surface. These connections act as conduits, facilitating the movement of immune cells back and forth.

The team of scientists found that these connections often traverse even through the outermost and toughest layer of membrane, the dura, opening up even closer to the brain surface than previously thought. To achieve these significant findings, the team utilized a specialized method called tissue clearing in combination with 3-D imaging to visualize the conduits.

During the tissue clearing process biological tissues are treated with a specific solution to render them transparent enabling the passage of light for the examination of both brain tissue and the skull under a microscope. As a result, 3-D images of structures and cells were generated, leading to a comprehensive visual analysis.

The research team probed even deeper into the distinct role the skull-based immune cells play in brain physiology and diseases. They began by questioning if the skull harbors unique brain-specific cells and molecules that cannot be found in other bones.

Extensive analysis of the RNA and protein content in the form of transcriptomics and proteomics analyses of both mouse and human bones affirmed this—the skull is indeed exceptional, hosting unique neutrophil immune cells, which are a type of white blood cell that play a critical role in the immune system's defense.

"These findings carry profound implications, suggesting a far more

complex connection between the skull and the brain than previously believed" highlights the first author of the study Ilgin Kolabas, Ph.D.-student at the Ertürk lab at Helmholtz Munich.

Ali Ertürk, corresponding author, adds, "This opens up a myriad of possibilities for diagnosing and treating brain diseases and has the potential to revolutionize our understanding of neurological diseases. This breakthrough could lead to more effective monitoring of conditions such as Alzheimer's and stroke, and potentially even aid in preventing the onset of these diseases by enabling early detection."

Envisioning a new future: From research to clinical practice

Another impactful finding was that using PET imaging, the researchers discovered that signals from the skull mirrored those from the underlying brain, with changes in these signals corresponding to disease progression in patients with Alzheimer's and stroke. Thereby showcasing a new potential to monitor brain inflammation simply by scanning the surface of the patient's head.

Looking forward, the researchers envision that their findings could translate to clinical practice in the form of non-invasive skull imaging. Ali Ertürk explains the impact on disease monitoring: "This could potentially be done using portable and wearable devices, offering a more accessible and practical way to monitor brain health." The team hopes that this approach will greatly improve the diagnosis, monitoring, and possibly even treatment of neurological disorders, bringing us a step closer to more effective management of these devastating conditions.

More information: Zeynep Ilgin Kolabas et al, Distinct molecular profiles of skull bone marrow in health and neurological disorders, *Cell*

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