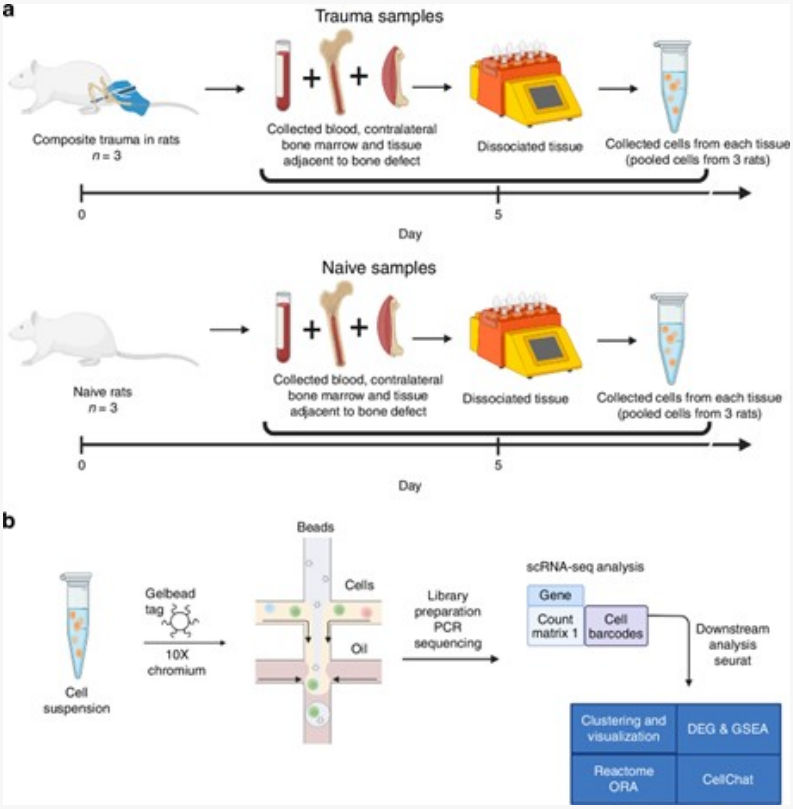
Study Uncovers How Immune Cells Contribute to Failed Bone Healing After Muscle-Bone Trauma

Using an integrated multi-tissue dataset, researchers identified two myeloid cell populations and marker genes driving immune dysregulation in polytrauma



Single-cell RNA sequencing is a powerful tool for studying the complex cellular interactions and underlying genetic influences at a single-cell resolution. By comparing the cells obtained from rats with polytrauma and naïve animals with no injury, the key

CHENGDU, SICHUAN, CHINA, July 21, 2025 /EINPresswire.com/ -- Gaining insights into the complex pathways and key cell populations involved in immune dysregulation can aid the development of therapeutic approaches to treat polytrauma, which is associated with poor patient outcomes. In a new study, researchers from the USA have utilized advanced genetic analysis tools and techniques to reveal the cellular and molecular processes involved in polytrauma-induced immune dysregulation. Their findings advance our current knowledge on polytrauma and indicate actionable targets to treat immune dysregulation.

Polytrauma, which involves multiple serious injuries occurring simultaneously, is associated with complex healing challenges. In such cases, bone regeneration is often compromised, accompanied by widespread immune system dysregulation. These effects may not surface immediately, but they commonly emerge later in recovery, contributing to increased treatment burden and poorer long-term outcomes.

While the immune system plays a crucial role in healing, its dysfunction in polytrauma remains poorly understood. Previous studies have explored immune activity either at the injury site or

within systemic tissues like blood and bone marrow. However, an integrated analysis of both local and systemic immune responses is essential to fully understand how immune dysregulation impairs recovery.

To address this gap, a team of researchers led by Professor Krishnendu Roy, Bruce and Bridgitt Evans Dean of Engineering at Vanderbilt University, conducted a comprehensive study using single-cell RNA sequencing (scRNA-seq). The research team, based at the Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology, collaborated with Professor Robert Guldberg from the Department of Bioengineering and Knight Campus for Accelerating Scientific Impact at the University of Oregon. This work was supported by a National Institutes of Health grant (R01AR074960). Their findings were published online in Bone Research on 07 July, 2025.

“Previously, our research group had developed a preclinical rat model of polytrauma that could mimic severe musculoskeletal trauma along with the associated local and systemic immune responses. In this study, we utilized cells from the polytrauma rat model and subjected them to scRNA-seq analysis to comprehensively assess the cellular and molecular mechanisms that drive immune dysregulation in polytrauma”, says Prof. Roy, sharing further details about the study.

The team combined scRNA-seq with differential gene expression (DEG) analysis, gene set enrichment analysis (GSEA), and the CellChat tool to identify the key immune cells involved. Their analysis revealed a prominent role of myeloid cells—a type of white blood cell—in shaping immune responses across the blood, bone marrow, and injured tissue.

Building on their previous findings linking systemic immunosuppressive myeloid cells with poor bone healing outcomes, the researchers sub-clustered the blood polytrauma myeloid cells into five distinct groups to identify those expressing immunosuppressive genes such as interleukins-4 (IL-4), IL-13, and IL-10. The clusters expressing these immunosuppressive genes were designated as trauma immunosuppressive myeloid (TIM) cells. Further DEG analysis revealed that TIM cells from polytrauma patients significantly expressed additional immunosuppressive genes, including annexin A1 (Anxa1) and nitric oxide synthase 2 (Nos2).

To decipher the pathways used by TIM cells to communicate with other myeloid cells, the team assessed ligand-receptor interactions using CellChat tool. Their analysis revealed that TIM cells were dependent on chemokine pathway involving Ccl6-Ccr1 and immunosuppressive Anxa1-Fpr2 mechanisms to communicate with other cells in polytrauma blood.

In the local injury site tissue affected during polytrauma, mono/mac cells demonstrated increased expression of pro-inflammatory genes including secreted phosphoprotein 1 (SPP1), fibronectin 1 (FN1), and Anxa2. Interestingly, the mono/mac cells showed reduced expression of tissue repair genes following polytrauma. By utilizing an integrated all-tissue dataset, the research team further discovered 15 closely connected hub genes which could potentially regulate polytrauma-induced immune dysregulation.

The altered communication patterns in polytrauma reveal the critical role of myeloid cell interactions, with TIM cells involved in immune suppression while mono/mac cells drive inflammatory pathways. Future studies can build on our findings to develop targeted strategies to modulate immune responses, reduce complications, and ultimately improve clinical outcomes in patients with polytrauma. Towards that goal, a multi-site clinical study to risk stratify patients with open tibial fractures has been initiated by Prof. Guldberg and colleagues.

In summary, this study not only advances our current understanding of complex immune interactions following polytrauma but also provides actionable targets for therapeutic intervention.

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Reference
Title of original paper: Single-cell transcriptomic analysis identifies systemic immunosuppressive myeloid cells and local monocytes/macrophages as key regulators in polytrauma-induced immune Dysregulation

Journal: Bone Research

DOI: 10.1038/s41413-025-00444-x

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