

Seeing obesity across the whole body: MouseMapper links cellular maps to mechanism

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Research related to obesity tends to focus primarily on a single organ or tissue. For instance, studies on adipose tissue center on inflammation, those on the liver focus on metabolic injury, and investigations of peripheral nerves target neuropathy. While this research approach facilitates practical experimentation, it may overlook organs or tissues that were not initially considered for study and hinders the revelation of interconnections between abnormalities in different tissues. In a recent *Nature* study, Kaltenecker and colleagues developed MouseMapper, a deep-learning framework that turns whole-mouse light-sheet images into quantitative maps of nerves, immune cells, organs and tissues.¹ Rather than treating image segmentation as an endpoint, MouseMapper links unbiased whole-body screening to targeted functional and molecular investigation (Figure 1).

Whole-body clearing and light-sheet microscopy can now render an intact adult mouse optically transparent and reveal labelled structures in three dimensions.² Nevertheless, image acquisition is no longer the primary bottleneck. A single scan can generate datasets of tens of terabytes. Meanwhile, nerve fibers span extensive distances, with fine terminal branches readily obscured by heterogeneous background signals; immune cells may also coalesce within densely packed regions. Extracting biologically meaningful information from such datasets is the greater challenge, and manual analysis

is unrealistic. Earlier automated methods showed that whole-body imaging could track processes such as tumour spread,³ but most were built for a limited target or a small set of predefined tissues.

MouseMapper addresses this problem through three linked modules. The Nerve-Module traces peripheral nerves and converts them into graphs that can be measured by branch number, length, thickness and connectivity. The Immune-Module detects CD68-positive cells and groups them into clusters of different sizes. The Tissue-Module assigns these signals to 31 organs and tissues, giving the cellular findings an anatomical address. By assigning each signal to a defined organ or tissue, the Tissue-Module turns an otherwise enormous collection of fluorescent pixels into an anatomically interpretable map.

Instead of training the Nerve-Module from scratch, the researchers fine-tuned VesselFM, a foundation model originally developed for three-dimensional blood-vessel segmentation.⁴ Although vessels and nerves have different biological functions, both form elongated, branching tubular networks, allowing the vascular model to provide a useful structural starting point. After fine-tuning, the model outperforms multiple models trained exclusively on annotated nerve data in detecting delicate nerve branches. It also generalizes to higher-resolution scans, antibody-labeled tissues, an alternative neuronal

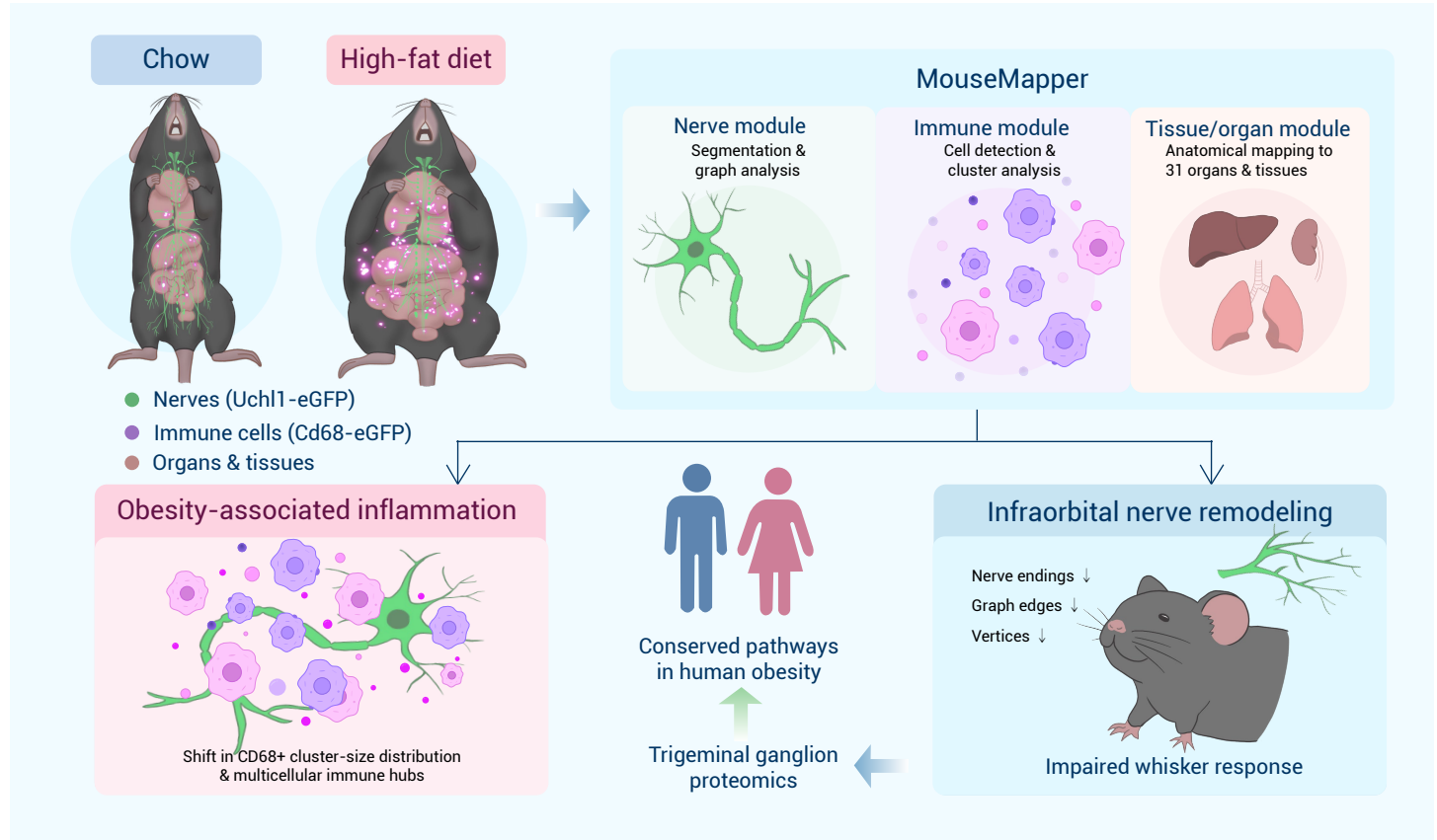


Figure 1. MouseMapper links whole-body imaging to functional and molecular discovery Whole-body clearing and light-sheet microscopy map nerves, CD68-positive immune cells and 31 anatomical compartments in chow-fed and obese mice. The framework reveals infraorbital nerve remodelling associated with impaired whisker responses and proteomic pathway changes, alongside tissue-specific shifts in CD68-positive cell clusters and multicellular inflammatory hubs.

reporter mouse line, and human embryonic nerve datasets. The immune model showed similar robustness across tissues and labelling methods. The model maintains consistent performance across varying imaging resolutions, labelling approaches, reporter lines and human embryonic datasets, indicating its outputs are not merely the result of overfitting to a single experimental condition. Nonetheless, further validation across broader datasets and experimental settings remains necessary.

Applied to diet-induced obesity, MouseMapper revealed that peripheral nerve remodelling was unevenly distributed across the body. Tissue expansion reduced nerve density in several regions, and graph analysis suggested a shift towards thinner nerve bundles. The most striking change appeared in the infraorbital nerve, a branch of the trigeminal nerve that supplies the whisker pad. Obese mice had 60.7% fewer nerve endings, 57.8% fewer graph edges and 57.6% fewer vertices than chow-fed controls. Yet the thickest part of the nerve was largely preserved. The preservation of the main nerve trunk, together with marked reductions in nerve endings, edges and vertices, is more consistent with a loss of distal branching complexity than with uniform degeneration of the entire nerve.

This structural abnormality coincided with diminished behavioral responses to whisker stimulation, establishing a link between infraorbital nerve remodelling and impaired sensory function. Investigations were subsequently extended to the trigeminal ganglion, where the cell bodies of these sensory neurons reside. Proteomic profiling detected over 6,000 proteins per sample and identified altered pathways associated with actin organization, RHO GTPase signalling, axon guidance, the complement system, ERBB signalling, and innate immunity. Changes involving SEPTIN7, SERPINA1 and ERK signalling were consistent with coordinated cytoskeletal and inflammatory remodelling, although their causal roles remain unresolved.

The researchers also analysed post-mortem human trigeminal ganglia. Several obesity-associated pathways overlapped with those found in mice, including axon guidance, cytoskeletal regulation, neurodegeneration and immune signalling. The overlap between mouse and human datasets is notable because the trigeminal system has received little attention in obesity research. However, the human analysis was limited to proteomic profiling of post-mortem trigeminal ganglia. It did not assess infraorbital nerve morphology or facial sensory function. The findings therefore indicate pathway-level concordance between species rather than direct evidence of an equivalent structural neuropathy in humans.

MouseMapper also provides a different view of obesity-associated inflammation. Instead of reporting only the total amount of CD68 signal, the authors asked how immune cells were arranged in space. High-fat feeding shifted the balance from small clusters towards medium or large clusters in several tissues, especially liver and visceral adipose tissue. In obese visceral fat, macrophage-rich aggregates were located near T cells, natural killer cells, antigen-presenting cells and blood vessels. These multicellular aggregates, many of which were located near blood vessels, indicate that obesity alters the spatial organization of tissue inflammation as well as immune-cell abundance.⁵

Unlike dissociation-based assays, whole-body imaging preserves the local neighbourhoods in which immune cells, stromal cells and blood vessels interact. Cluster size, however, is not equivalent to immune activation, because it also depends on cell density, reporter intensity, imaging resolution and segmentation parameters. CD68 is also a broad marker that cannot distinguish among the diverse functional states of macrophages. The immune map is therefore better suited to hypothesis generation than to cell-state assignment. Regions containing unusually large or spatially organized clusters can subsequently be examined using multiplex imaging, spatial transcriptomics or targeted perturbation.

The biological conclusions remain constrained by imaging resolution, labelling efficiency and cohort size. The standard whole-body scans have a lateral resolution of about 5.9 micrometres, which is not enough to resolve the finest axons, synaptic boutons or complete terminal arbors. Higher-resolution imaging improves detail but can produce datasets of up to 50 terabytes per mouse. The biological readout also depends on reporter expression and antibody penetration, both of which may vary between tissues and between lean and obese animals. The animal groups were small and included only

male mice, while the human comparison involved five lean and four obese post-mortem donors with heterogeneous clinical backgrounds. Whether the reported neural and immune phenotypes extend to female animals, other ages and alternative models of obesity remains to be determined. Their prevalence and clinical relevance will also require evaluation in larger and more diverse human cohorts. These limitations also delineate the subsequent work required for translational research. The present study employed male mice fed a high-fat diet, whereas the human-related analysis utilized only a small number of postmortem human trigeminal ganglion samples. Accordingly, the reproducibility of the neurological and immune phenotypes needs to be validated across different sexes, ages, and additional obesity models, followed by verification in larger-scale human cohorts. Since whole-body tissue clearing and imaging constitute an endpoint detection method, it is necessary to establish intervention groups and collect samples at different stages of the disease to determine whether the aforementioned abnormalities can be prevented or reversed. Subsequent work may conduct targeted functional experiments and spatial molecular atlas analysis on the tissues identified by MouseMapper, thereby distinguishing correlation from causation and screening for key pathways amenable to therapeutic investigation. Therefore, MouseMapper itself is not a diagnostic or therapeutic tool. Its immediate practical value lies in narrowing the scope of research screening, directing attention toward previously overlooked tissues, and providing a general anatomical framework for evaluating systemic pathological changes as well as the efficacy of candidate interventions.

MouseMapper shifts whole-body imaging from descriptive visualization towards hypothesis-generating analysis. In this workflow, unbiased anatomical mapping can identify an unexpected phenotype, which can then be prioritized for quantitative, functional and molecular investigation. Trigeminal nerve remodelling provides a useful example: a previously overlooked anatomical change emerged from the whole-body survey and was subsequently linked to impaired sensory function and molecular alterations in the trigeminal ganglion. Similar workflows may prove useful in diseases with spatially dispersed pathology, including metastatic cancer, systemic infection and neurovascular disorders. The broader contribution of MouseMapper lies less in any single segmentation module than in its ability to connect whole-body screening with experimentally testable biological mechanisms.

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Mengcheng He and Xiaozhuo Tan wrote the manuscript. Yikai Shao and Qiyan Yao supervised the whole process and revised the manuscript. Mengcheng He designed and drew Figure 1 in the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.