regions such as the stomach, small intestine and proximal colon? If so, and if the same type of immune response occurs in other gut locations, different sensory nerves might be activated there, triggering different symptoms, such as nausea, discomfort and bloating, that are relevant to other gut-pain disorders, for example a condition called functional dyspepsia[4].

Aguilera-Lizarraga and colleagues' work presents numerous potential options to consider for therapeutic intervention. These include: improving intestinal-barrier function to reduce gut access to the intestinal immune system; targeting IgE antibodies that are specific to the food substance of interest; reducing mast-cell degranulation; targeting molecules released by mast cells or the receptors on which they act; and blocking the colonic sensory nerves that transmit the noxious information and cause pain.

From a dietary point of view, can oral tolerance, once lost, be reacquired? In this regard, food-allergy studies suggest that eliminating the offending foods from people's diets, and then gradually reintroducing them, can improve the long-term prognosis[11]. Exclusion diets are increasingly popular for remedying gastrointestinal symptoms, including gluten-free diets for coeliac disease and, for IBS, diets low in a group of carbohydrates that are not completely digested or absorbed in the intestine (called FODMAPs — fermentable molecules of oligosaccharides, disaccharides, monosaccharides and polyols)[12]. Aguilera-Lizarraga and colleagues' study provides information on the mechanisms underlying abdominal pain, and gives added meaning to the saying, 'you are what you eat'.

Stuart M. Brierley is in the College of Medicine and Public Health, Flinders Health and Medical Research Institute, Flinders University, Adelaide, South Australia 5042, Australia, and at the Hopwood Centre for Neurobiology, South Australian Health and Medical Research Institute, Adelaide.
e-mail: stuart.brierley@flinders.edu.au

1. Basbaum, A., Bautista, D. M., Scherrer, G. & Julius, D. *Cell* **139**, 267–284 (2009).
2. Aguilera-Lizarraga, J. *et al. Nature* **590**, 151–156 (2021).
3. Kobayashi, T. *et al. Nature Rev. Dis. Primers* **6**, 74 (2020).
4. Enck, P. *et al. Nature Rev. Dis. Primers* **2**, 16014 (2016).
5. Mars, R. A. T. *et al. Cell* **182**, 1460–1473 (2020).
6. Grundy, L., Erickson, A. & Brierley, S. M. *Annu. Rev. Physiol.* **81**, 261–284 (2019).
7. Nowak-Wegrzyn, A., Szajewska, H. & Lack, G. *Nature Rev. Gastroenterol. Hepatol.* **14**, 241–257 (2017).
8. Mowat, A. M. *Nature Rev. Immunology.* **18**, 405–415 (2018).
9. Thammavongsa, V., Kim, H. K., Missiakas, D. & Schneewind, O. *Nature Rev. Microbiol.* **13**, 529–543 (2015).
10. Spiller, R. & Garsed, K. *Gastroenterology* **136**, 1979–1988 (2009).
11. Yu, W., Hussey Freeland, D. M. & Nadeau, K. C. *Nature Rev. Immunol.* **16**, 751–765 (2016).
12. Moayyedi, P., Simrén, M. & Bercik, P. *Nature Rev. Gastroenterol. Hepatol.* **17**, 406–413 (2020).

This article was published online on 13 January 2021.

Developmental biology

A molecular handbook for human development

Felicia Kuperwaser & Itai Yanai

A large-scale, high-resolution cell atlas of gene expression and regulation in human embryos enables innovative investigation of development through multi-organ and multi-modal analysis.

Charles Darwin developed his theory of natural selection by comparing features between individuals and species. A comparative approach is also crucial to establish the cellular taxonomy that underlies human physiology. Technological advances in single-cell genomics have facilitated the production of numerous cell atlases that, through comparative analysis, define the full set of cells that constitute a system of interest — usually a whole organ[1]. Extending the scope of an atlas from organ to whole organism increases the power of this approach by capturing data across physiological systems. To this end, two papers in *Science* present the comprehensive molecular characterization of cell types across nearly all organs during human fetal development[2,3]. They reveal previously unidentified cell subtypes, and define cell-differentiation pathways through analysis of gene expression and chromatin (the DNA–protein complex into which a cell's genetic material is packaged).

The work is a remarkable feat, both technically, in terms of the complexity of the paired data, and because of the scale of the studies, which involved analysis of 15 organs from human fetuses between 72 and 129 days after conception. In the first of the papers, Cao *et al.*[2] generated gene-expression profiles (transcriptomes) from 4 million single cells across these organs. Analysis of these profiles revealed 77 main cell types, defined with reference to existing single-organ atlas data.

In the second of the papers, Domcke *et al.*[3] presented an improved method for assessing chromatin accessibility, an analysis that provides insight into how genes are regulated during development. Loosely packaged chromatin regions are thought to be more accessible to regulatory proteins such as transcription factors, and are often involved in regulating gene expression and in establishing and maintaining cell identity. The authors' approach enabled the analysis of 800,000 cells from the same samples as those used by Cao and colleagues, which led to the identification of 54 of the same cell types.

The considerable data collected allowed both groups to define highly expressed 'marker' genes and corresponding transcription factors unique to each cell type. The authors also integrated their atlases with existing mouse atlas data[4], making each a more robust and complete reference. Combining these data sets enables validation of how cell types are characterized in each species and will help researchers to better design experiments that use mouse models to investigate human physiology. Together, the papers constitute a substantial resource, which is openly available on an interactive website (descartes.brotmanbaty.org).

The authors developed an analytical framework that led to interesting biological insights, demonstrating the potential of this body of

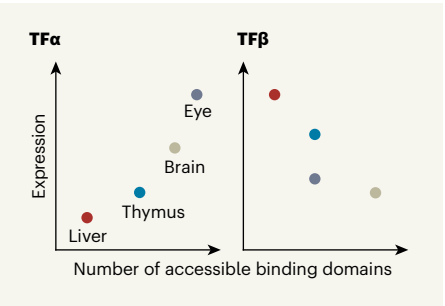

Figure 1 | Combined data types in a cell atlas for human development. A new cell atlas of human development combines data on gene expression[2] and chromatin accessibility[3] (chromatin is the DNA–protein complex in which DNA is packaged — 'looser' packaging makes DNA accessible to regulatory proteins such as transcription factors) in cells across 15 developing organs. The researchers combined these data to study the roles of transcription factors in human development, by cataloguing the expression of transcription factors of interest and the presence of their binding domains in accessible chromatin in each cell type. Transcription factors for which expression positively correlated with the presence of binding domains (such as TFα in this example) were assigned as transcriptional activators, whereas a negative correlation (as with TFβ) suggested a role as transcriptional repressors.

work for making discoveries. They defined previously uncharacterized cell subtypes by comparing expression and chromatin patterns across organs, and they used this multi-organ approach for cell-lineage analysis.

Domcke *et al.* compared cell-lineage diversity across organs and revealed that circulating blood cell subtypes are almost identical, irrespective of the organ from which they were isolated. Conversely, they found that endothelial cells (key components of blood vessel walls) are regulated by many tissue-specific factors and differ by organ. Therefore, in trying to understand functional relationships between these subtypes and other cells during development, tissue context might figure more prominently in endothelial cell variability than it does in other lineages. Cao *et al.* precisely annotated three subtypes of red blood cell (erythroid) progenitor, each representing a different stage of maturation, and measured their presence across organs. They identified early erythroid progenitors in the adrenal gland, a previously unknown site of erythroid development, which might bridge the developmental switch in the site of production of these cells from fetal liver to bone marrow.

Domcke and colleagues also used the paired data sets to assess the relationship between gene expression and its regulation. They identified previously unknown transcription factors specific to discrete developmental stages by analysing transcription-factor binding sites in accessible chromatin regions. Then, on the basis of the relationships between expression of cell-type-specific transcription factors and binding-site availability, they assigned putative functions to these transcription factors as activators or repressors (Fig. 1).

These studies represent the next generation of atlas papers. Currently, standard cell atlases characterize a single organ on a molecular level using one data modality. The new work provides a road map for unifying these disparate data sets.

A limitation of the work is that the current atlases correspond only to a specific developmental window, and not every organ is included. However, the atlas can be expanded with the integration of new data, and the growing resource will be an asset to biologists in standardizing cell types across development. Unidentified cells are typically characterized in relation to the other cell types of that organ, but these definitions might vary between data sets. Multi-organ analysis creates a consistent framework of characteristic cell types against which to compare new data. It can match unidentified cells with corresponding cell types in another organ on the basis of shared expression patterns or, conversely, it can highlight tissue-specific differences between previously grouped cells.

Standardization in the field will yield a more refined, uniform and valuable resource that will facilitate exploration of new questions. For example, it will help researchers to investigate how cells of a given lineage differ depending on tissue-intrinsic properties or dynamic lineage changes. Immune cell expression and function might differ, for instance, depending on the organs they target or on changes in their site of production.

Although the data presented capture healthy development, characterization of these tissues also has implications for the study of disease. For example, this resource will help to enhance our basic understanding of stem-cell differentiation by identifying key regulators of cell fate and development. This, in turn, will aid in the analysis of lineage dysregulation in developmental disorders. Its utility will also extend to investigating adult diseases characterized by changes in cell state and differentiation, such as cancer, degenerative disease and ageing. Ultimately, these comparisons, both to disordered development and to diseased adult tissue, might reveal targets for therapeutic intervention as well as fundamental principles of human physiology and development.

Felicia Kuperwaser and **Itai Yanai** are at the Institute for Computational Medicine, New York University, Grossman School of Medicine, New York, New York 10016, USA.
e-mails: felicia.kuperwaser@nyulangone.org; itai.yanai@nyulangone.org

1. Aldridge, S. & Teichmann, S. A. *Nature Commun.* **11**, 4307 (2020).
2. Cao, J. *et al. Science* **370**, eaba7721 (2020).
3. Domcke, S. *et al. Science* **370**, eaba7612 (2020).
4. Cao, J. *et al. Nature* **566**, 496–502 (2019).

This article was published online on 25 January 2021.

Ageing

Immune-cell shutdown harms old brains

Jonas J. Neher

Immune cells called macrophages have been found to shut down major metabolic pathways during ageing. Restoring metabolism in these cells is sufficient to alleviate age-associated cognitive decline in mice. **See p.122**

Immune cells called macrophages are found in almost every tissue, and are crucial for maintaining organ health and providing a first line of defence against disease-causing organisms. The energy demands of macrophages increase drastically when they are activated, and so they rebalance or enhance their two main energy-producing metabolic pathways (glycolysis and oxidative phosphorylation) to quickly fuel an effective immune response[1]. Minhas *et al.*[2] report on page 122 that macrophages shut down these metabolic pathways during ageing, severely compromising macrophage function and, in turn, brain health. This work has implications not only for the preservation of brain health during ageing, but also for conditions such as Alzheimer's disease or sepsis, in which similar maladaptive macrophage states could be common.

As we age, chronic, low-grade inflammation develops in most people[3]. One inflammatory signalling protein whose levels rise not only during ageing[4] but also during neurodegenerative disease[5] is prostaglandin E_2 (PGE_2). Minhas *et al.* set out to investigate whether PGE_2 might cause age-associated changes in macrophages. Interestingly, the authors found increased production of PGE_2 in human and mouse macrophages themselves — both in the brain and elsewhere in the body (the periphery). This led to the activation of PGE_2's receptor protein EP2 in the cells, which in turn resulted in suppression of oxidative phosphorylation and glycolysis. The resulting energy-deficient state both limited the beneficial functions of macrophages and increased inflammation.

To determine whether these changes could cause age-associated cognitive dysfunction, the authors examined a mouse strain in which EP2 receptor levels were reduced exclusively in macrophages in the body and brain, and treated mice with an EP2 inhibitor. Strikingly, EP2 inhibition restored macrophage metabolism to youthful levels in both settings, reducing inflammation in the periphery and brain, and alleviating cognitive decline (Fig. 1). These results indicate that (at least in mice) macrophage dysfunction during ageing affects brain health, and that normal cell function can be restored by reversing metabolic shutdown in the cells.

Minhas and colleagues went on to dive deeper into the metabolic rewiring of aged