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Impact of the Human Cell Atlas on medicine

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Single-cell atlases promise to provide a 'missing link' between genes, diseases and therapies. By identifying the specific cell types, states, programs and contexts where disease-implicated genes act, we will understand the mechanisms of disease at the cellular and tissue levels and can use this understanding to develop powerful disease diagnostics; identify promising new drug targets; predict their efficacy, toxicity and resistance mechanisms; and empower new kinds of therapies, from cancer therapies to regenerative medicine. Here, we lay out a vision for the potential of cell atlases to impact the future of medicine, and describe how advances over the past decade have begun to realize this potential in common complex diseases, infectious diseases (including COVID-19), rare diseases and cancer.

Disease occurs as a result of aberrations in cells and cellular ecosystems within tissues — driven by genetic variations as well as environmental impacts, from nutrients to pathogens. To understand pathogenesis and discover and deliver new treatments, we need to understand cells, their internal circuits, and their interactions in health and disease. Although this has been appreciated for many decades, technical challenges have limited our ability to simultaneously probe human disease at a large scale and at high molecular and cellular resolution.

Breakthroughs in single-cell and spatial genomics in the past decade have opened the way to single-cell and tissue atlases in health and disease (Table 1), and are poised to impact every aspect of medicine (Fig. 1). These include understanding the cell types and programs in which disease genes act, deciphering mechanisms of disease initiation and progress at the cellular and multicellular levels, defining new signatures for disease monitoring and diagnosis, and discovering and developing new molecular, gene and cell therapies and tracking their impact in patients.

As disease is only fully understood in reference to health, and vice versa, achieving this vision will require comprehensive reference maps of all human cells as a basis for both understanding human health and diagnosing, monitoring and treating disease. Mapping human cells poses major logistical and technical challenges, which are being met by the international Human Cell Atlas (HCA) initiative[1]. When the HCA was being planned, the initial members of the HCA community laid out our plans and goals in a white paper[2], stating an ambition to accelerate biomedical research, drug discovery and development, and medical practice by fostering both curiosity-driven research and its clinical applications.

Less than a decade since the emergence of single-cell profiling methods, and 5 years since the launch of the HCA, the field has made enormous strides in delivering findings that are relevant to human health, with rapid development and application of new methods to tackle medical questions (Table 1 and Fig. 2). In particular, our community, like many others, was galvanized by the global challenge of the COVID-19 pandemic to contribute early information about the cells that are most susceptible to infection[3–5], and later to characterize the impact of SARS-CoV-2 infection on tissues throughout the body[6,7] (Box 1). Here, we explore the key ways in which cell atlases are accelerating biomedicine and their future potential.

Understanding disease biology: from genes to cells, programs and tissues

From disease-associated genes to cells of action

Genetic variants — both common and rare — contribute to the risk of developing disease, and human genetic studies have identified more than 100,000 variants associated with different human traits, especially the risk of developing different diseases. However, to understand the role of these variants in disease, we must understand the cells in which they are expressed and act. In rare diseases, the relevant cell type may be unknown, or even undiscovered. In common complex diseases, the candidate loci from genome-wide association studies (GWAS) and phenome-wide association studies are often in non-coding regions

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Table 1 | A selection of key experimental methods for construction of cell atlases at different levels of biological organization

1. Clinical data	
Clinical-trial data; health records; disease registries; patient registries	
2. Tissue imaging and histology	
Medical and biomedical	
Computed tomography (CT); computed axial tomography (CAT)	
Magnetic resonance imaging (MRI)	
Magnetic resonance spectroscopy (MRS)	
Positron emission tomography (PET); single-photon emission computed tomography (SPECT)	
Photoacoustic imaging	
Ultrasound	
X-rays	
Microscopy	
Optical imaging: fluorescence/confocal; light-field; light-sheet; multiphoton; super-resolution; spectroscopy	
Bioluminescence	
Atomic force microscopy	
Electron microscopy	
3. Spatial (platform, description)	
RNA	
CosMx; GeoMx	In situ multiplex RNA
DNA microscopy	
ExSEQ	Expansion sequencing
FISSEQ	Fluorescent in situ RNA-sequencing
Geo-seq	Geographical position sequencing
INSTA-seq	In situ transcriptome accessibility sequencing
ISS	In situ sequencing
smFISH	Single-molecule fluorescent in situ hybridization (FISH)
MERFISH; osmFISH; SeqFISH	Multiplexed smFISH
PLISH	Proximity ligation in situ hybridization
Spatial transcriptomics; HDST; Slide-seq; Visium	Slide-based spatial transcriptomics
STARMap	Spatially resolved transcript amplicon readout mapping
TIVA-seq	Transcriptome in vivo analysis
Protein	
CODEX; CosMx; GeoMx; ImmunoSABER	Multiplex protein detection
MIBI	Multiplex ion beam imaging
Multiplex IF	Multiplex immunofluorescence
tCy-CIF	Tissue-based cyclic immunofluorescence
4. Multimodal (platform, description)	
ASAP-seq	Assay for transposase-accessible chromatin sequencing (ATAC) with select antigen profiling
CITE-seq	Cellular indexing of transcriptomes and epitopes by sequencing
Perturb-seq; CRISP-seq; CROP-seq;	Pooled CRISPR screen with single-cell RNA-seq readout
DOGMA-seq	Single-cell RNA, protein, mtDNA, + ATAC-seq
DR-seq	gDNA–mRNA sequencing
ECCITE-seq; Perturb-CITE-seq	Pooled CRISPR screen with single-cell RNA-seq and protein readout
G&T-seq	Genome and transcriptome sequencing
InCITE-seq	Single-nucleus RNA-seq and proteins
ORCA	Optical reconstruction of chromatin architecture
Paired-seq	Single-cell RNA and DNA accessibility seq
Perturb-ATAC	Pooled CRISPR screen with single-cell ATAC-seq readout
PHAGE-ATAC	Phage-based multiplex protein measurements and single-cell ATAC-seq
REAP-seq	Single-cell RNA-seq and proteins
scCAT-seq	Single-cell chromatin accessibility and transcriptome sequencing
scCOOL-seq	Chromatin overall omic-scale landscape sequencing
sciCAR	Single-cell combinatorial indexing chromatin accessibility and mRNA
scMethyl-HiC	Single-cell methyl and high-throughput chromosome conformation capture
scM&T-seq	Single-cell methylome and transcriptome sequencing
scNMT-seq	Single-cell nucleosome, methylation, and transcription sequencing
scNOMeRe-seq	Single-cell nucleosome occupancy, methylome, and RNA expression sequencing
scTrio-seq	Single-cell triple omics sequencing
snm3C-seq	Single-nucleus methyl-3C sequencing
SHARE-seq	Single-cell RNA- and ATAC-seq
SIDR-seq	Simultaneous isolation of genomic DNA and total RNA
SNARE-seq	Single-nucleus chromatin accessibility and mRNA expression sequencing
snmCT-seq	Single-nucleus methyl cytosine and transcriptome sequencing
5. Transcriptomics (platform, description)	
CEL-seq	Single-cell RNA-seq by multiplexed linear amplification
Chromium	
Cyto-seq	Cytometry-based sequencing
DRoNC-seq	Massively parallel sNuc-seq with droplet technology
Drop-seq; inDrop	Single-cell RNA-seq with droplet technology
LCM-seq	Laser-capture microdissection coupled with PolyA-based RNA-seq
Live-seq	Transcriptome profiling of living cells after cytoplasmic biopsy
MARS-seq	Massively parallel single-cell RNA-seq
MATQ-seq	Quantitative single-cell RNA-seq
QUARTZ	
scifiRNA-seq	Single-cell combinatorial fluidic indexing RNA-seq
sciRNA-seq	Single-cell combinatorial indexing RNA-seq

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Table 1 (continued) | A selection of key experimental methods for construction of cell atlases at different levels of biological organization

seq-Well	Single-cell RNA-seq with microwells
SLAM-seq	Metabolic mRNA sequencing (thiol (SH)-linked alkylation for metabolic sequencing of RNA)
SMART-seq	Switching mechanism at the end of the 5′-end of the RNA transcript sequencing
SPLiT-seq	Split-pool ligation-based transcriptome sequencing
STRT-seq	Single-cell tagged reverse transcription sequencing
SUPeR-seq	Universal poly(A)-independent RNA-sequencing
VASA-seq	Vast transcriptome analysis of single cells by dA-tailing
6. Genome and epigenomics (platform, description)	
Genome	
LIANTI	Linear amplification via transposon insertion
MALBAC	Multiple annealing and looping-based amplification cycles
MDA	Multiple displacement amplification
scDNA-seq	Single-cell DNA-sequencing
SMOOTH-seq	Single-molecule real-time sequencing of long fragments amplified through transposon insertion
SMRT-DNA-seq	Single-molecule real-time DNA-sequencing
DNA methylation	
scAba-seq	Single-cell restriction endonuclease AbaSI sequencing
scBS-seq	Single-cell bisulfite sequencing
scCGI-seq	Single-cell CpG island methylation sequencing
scMethyl-seq	Single-cell methylation sequencing
scRRBS	Single-cell reduced-representation bisulfite sequencing
TAB-seq	Tet-assisted bisulfite sequencing
Histone modification	
scChIC-seq	Single-cell chromatin immunocleavage sequencing
scChIP	Single-cell chromatin immunoprecipitation followed by sequencing
CoBATCH	Combinatorial barcoding and targeted chromatin release
DAM-ID	DNA adenine methyltransferase identification
iACT-seq	Antibody-guided chromatin tagmentation sequencing
scChIL-seq	Single-cell chromatin integration labeling
scCUT&RUN	Single-cell cleavage under targets and tagmentation
Chromatin structure	
FAIRE-seq	Formaldehyde-assisted isolation of regulatory elements sequencing
NOME-seq	Nucleosome occupancy and methylome sequencing
scATAC-seq	Single-cell sequencing assay for transposase-accessible chromatin
sciATAC-seq	Single-cell indexing ATAC-seq
scDNase-seq	Single-cell DNase I hypersensitive sites sequencing
scMNase-seq	Single-cell micrococcal nuclease sequencing
scTHS-seq	Single-cell transposome hypersensitive site sequencing
3D organization	
scHi-C	Single-cell high-throughput chromosome conformation capture

that are difficult to connect to the affected protein-coding gene, cell of action or function. Moreover, even when common and rare diseases have similar clinical phenotypes, these could be the results of variants in different genes, thus making it more challenging to identify common mechanisms at the pathway or cellular level.

Cell atlases provide a way to tackle each of these challenges (Fig. 1). In rare Mendelian genetic disorders, healthy tissue atlases have led to the discovery of novel cell types, including rare ones, that uniquely express key disease genes, and have even corrected long-held assumptions. For example, the pulmonary ionocyte – a novel, rare cell type discovered in cell atlases of the trachea – is the main cell type expressing *CFTR*[8,9], the causal gene in cystic fibrosis. In particular, studies in the Human Developmental Cell Atlas (HDCA) can shed light on Mendelian disorders that manifest at birth, such as the cellular origins of different Hirschsprung's disease variants in the developing[10] versus adult[11] enteric nervous system, or the impact of trisomy 21 on bone marrow hematopoietic stem cells and their niche[12].

In common complex diseases, similar analyses have related disease genes in associated loci to specific cell subsets across many inflammatory[13–16], autoimmune[17–19], neurodegenerative[20–23], respiratory[8,24], fibrotic[25,26] and other[27,28] diseases, using both healthy and disease atlases of the relevant tissue, and revealing novel unexpected associations. For example, integrating the extensive GWAS literature for ulcerative colitis (UC) with single-cell atlas data enabled the identification of key cell types expressing genes associated with UC by GWAS, including epithelial M-like cells – which are exceedingly rare in the healthy colon, but expanded significantly in the inflamed, diseased colon[29]. Because most risk variants are in non-coding regions[30], integration of GWAS summary statistics, single-cell profiles and chromatin data[8,9], as well as joint profiling of chromatin and RNA in single cells[31], can further facilitate the discovery of such associations[32]. One such analysis showed that not only is a specific gene program induced in colonic M cells in UC, accounting for overall disease risk heritability, but that common variants in the *FERMT1* locus (a gene implicated in a rare form of inflammatory bowel disease (IBD)[33]) contribute substantially to this association[34]. Moreover, because common disease genes are often pleiotropic, broader cross-tissue atlases can help to better decipher their impact throughout the body[35–38]. Finally, atlases also allow us to move from the level of individual risk genes to the modules and programs in which they participate, thus helping decipher gene function, nominate causal processes, and related diseases with similar morbidities at the level of programs, even when the underlying genes are distinct[29]. This is illustrated in monogenic and polygenic IBD[39], in which programs involving M cells are enriched in both forms of the disease[39]. Single-cell atlases can also reveal cellular subtypes that are shared across tissues or are unique in particular locations or disease contexts, such as recent surveys of mouse[40] and human[41] fibroblasts.

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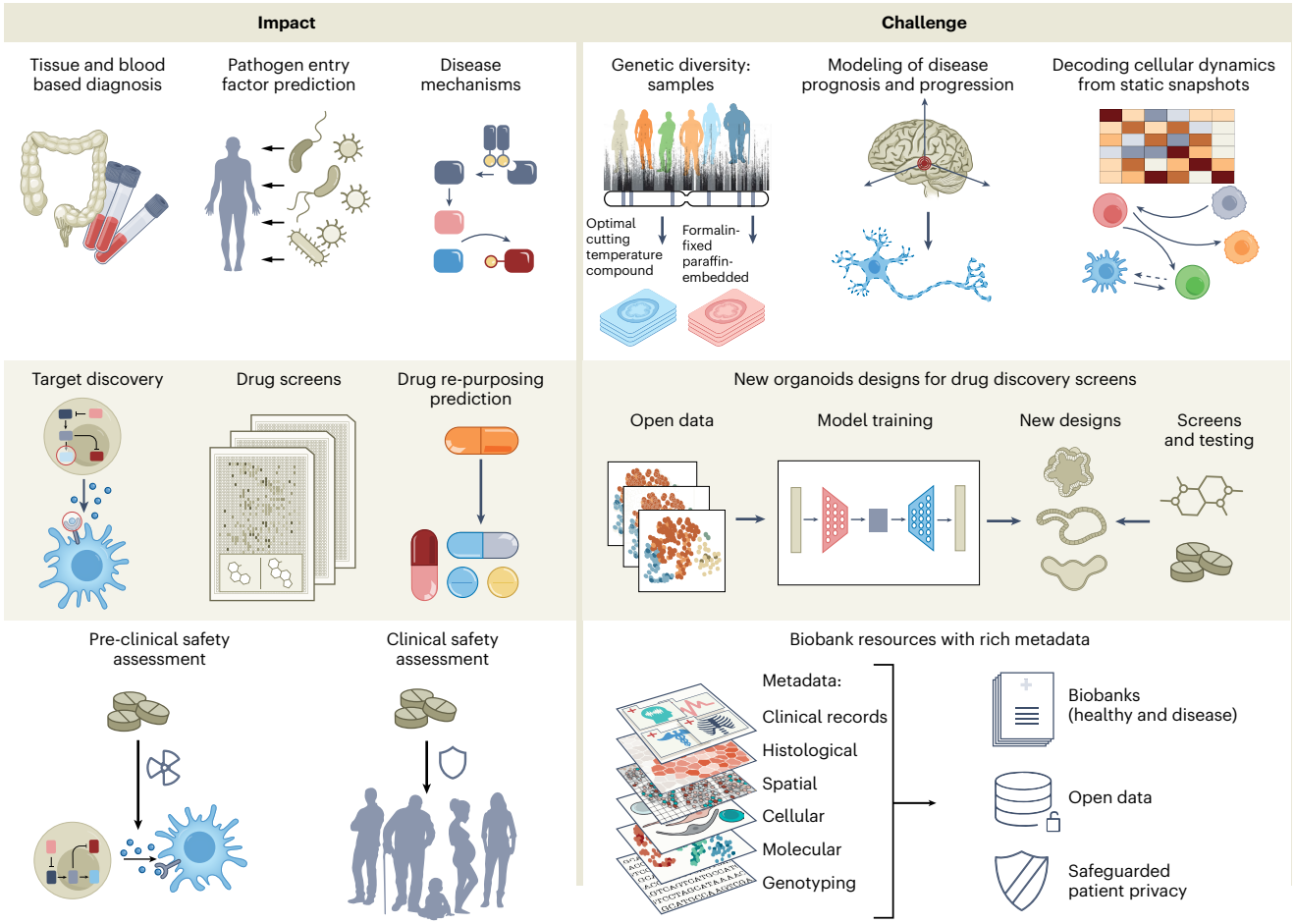

Fig. 1 | Potential medical impacts of the Human Cell Atlas and remaining challenges. Left, important insights that have been drawn from cell atlases on disease mechanisms, diagnosis and treatment. Right, key remaining technical and fundamental barriers for medical impact, including diversity, data availability and understanding disease progression.

Remodeling of cellular composition and multicellular architecture in disease tissue

Both cell-intrinsic and cell-extrinsic changes have key roles in pathogenesis and can be targeted by therapies, but changes in the cell's internal programs and shifts in cellular composition are often confounded in bulk profiling. The cellular — and increasingly spatial — resolution provided by atlases distinguishes these contributions and allows more accurate and sensitive comparison between health and disease, as shown in studies in IBD, asthma, pulmonary fibrosis, rheumatoid arthritis, diabetic kidney disease, cardiomyopathy, Alzheimer's disease and many other common diseases[24,29,40–51].

Both compositional and cell-intrinsic expression changes can be coordinated across multiple cell types, resulting in shifts in multicellular communities in disease. For example, comparing cellular composition in the ileum of patients with Crohn's disease with the healthy reference atlas identified a unique multicellular community of immune and stromal cells, which was predictive of a lack of response to anti-TNF therapy[42]. Comparison with healthy references also helps decipher the mechanisms driving these coordinated communities, and the gene programs within their constituent cells. For instance, compared with healthy tissue, atopic dermatitis and psoriasis skin lesions are characterized by the expansion of particular classes of macrophages and vascular endothelial cells that interact via the chemokine CXCL8 and its receptor ACKR1, respectively[52]. This interaction, which is suggested to promote lymphocyte recruitment, represents the re-emergence of a prenatal cellular program in disease tissue[52]. Finally, computational methods[53–55] can now recover multicellular gene programs, where cell-intrinsic programs are coordinated between multiple different cell types across samples or physical niches. Examples include a multicellular program across five cell types implicating several disease risk genes for UC[54], and the coordination of neurotransmission, cell adhesion, and development gene expression across cell types in the cortex in epilepsy[53].

Mapping malignant and microenvironment cells in tumors

Our understanding of human cancer biology is also being transformed by single-cell and spatial genomic atlases. Analysis of solid tumors in comparison with healthy references helps to chart their biological complexity — combining genetic and epigenetic variation within the malignant compartment with the diversity of cells in the tumor microenvironment, including immune[56–65], stroma[57,66] and even neural[67] cells, and their spatial organization[68]. This has helped identify relevant disease mechanisms[69,70] and opportunities for therapeutic interventions[58], as well as resistance mechanisms[71], including cell communities that may predict response to therapies such as checkpoint inhibitors[64,65] or chemoradiation[72], and the cell of origin in both adult and pediatric tumors[73–75] (determined in reference to healthy adult, developmental and pediatric atlases). As a brief illustrative example, in the specific context of interactions between malignant and immune cells in melanoma, studies have characterized the immune compartment, malignant cells, or both at different disease grades and with different treatment histories, describing dysfunctional versus stem-like T cell states associated with tumor resistance or reactivity[76,77], recovering malignant cell programs impacting T cell excluded phenotypes[58,78], and generalizing some of these findings to other tumor types[59,63].

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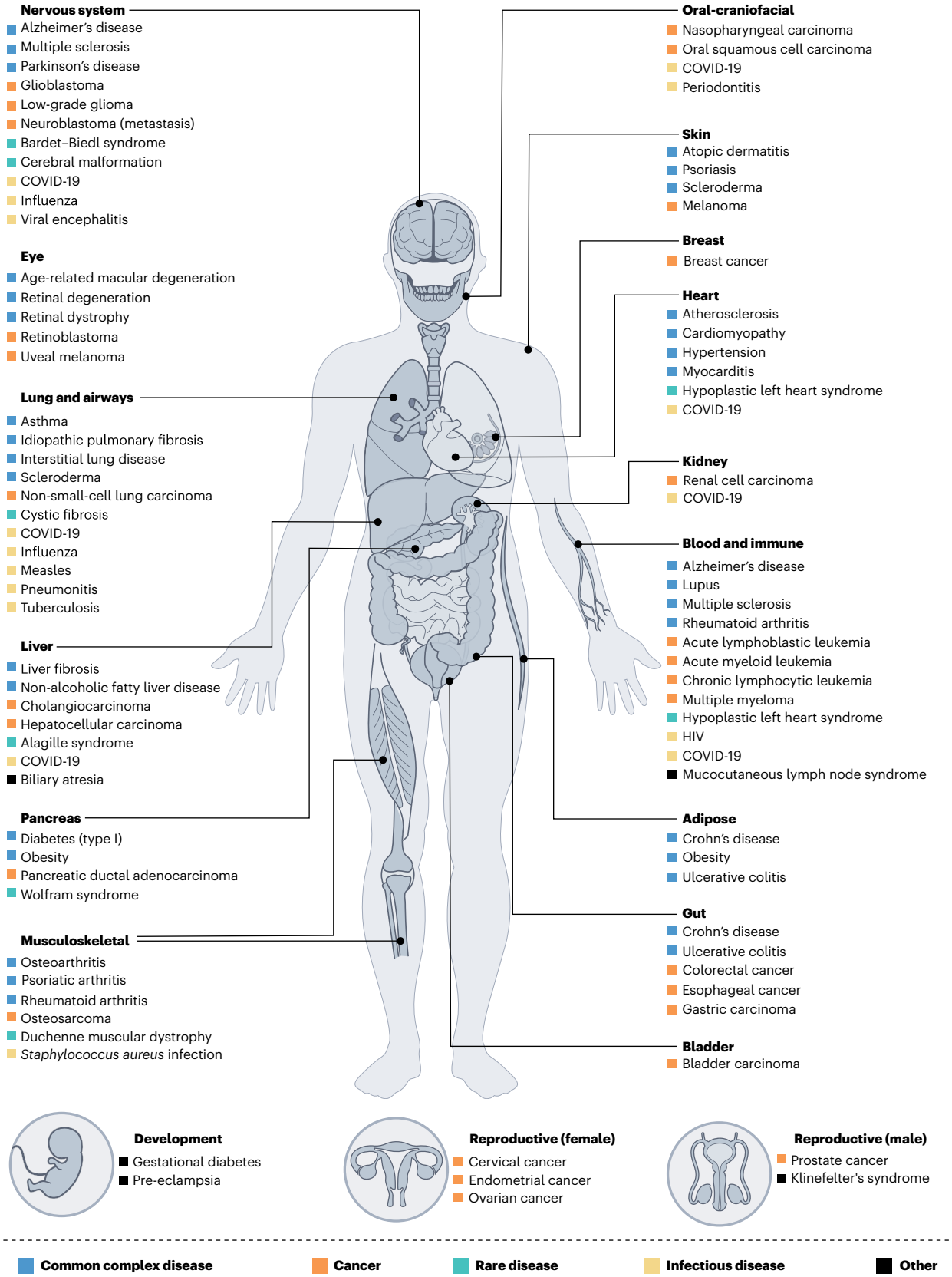

Fig. 2 | Single-cell atlases have been collected for a broad range of organs and disease tissues. Shown are the key organs and systems for which healthy tissue has been profiled by the Biological Networks of the Human Cell Atlas initiative (bold), and for which corresponding studies collected atlases of disease tissue from the same organ from people with common complex diseases (blue), tumors (orange), rare diseases (green), infectious diseases (yellow), or other conditions (black).

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BOX 1

COVID-19: a case study for single-cell agility

The COVID-19 pandemic demonstrated the agility and transformative impact of single-cell genomics — and the HCA community — in tackling a new disease. Early in the pandemic, HCA researchers quickly leveraged pre-existing reference maps of healthy human tissues to understand the underlying biology of this novel disease, and they harnessed single-cell and spatial genomics to rapidly initiate new studies in patients with COVID-19. This research was accelerated by the HCA's existing community structures and a strong commitment to data sharing and open science[2,138].

By spring 2020, studies had identified potential routes of infection, including the nasal epithelia and oral tissue, using existing data[5,139–141]. This was later confirmed in depth[142] and expanded to show the surprisingly broad range of tissues and cells that are accessible to the virus and are associated with epidemiological features[3]. A recent investigation into the increased infectivity and reduced pathogenicity of the Omicron BA.1 variant correlated its preferential replication in cells of the upper airway with reduced expression of the transmembrane protein TMPRSS2 in these cells — TMPRSS2 expression is highest within the lung[143].

Pivoting quickly to study patient samples once they became available, HCA researchers compared atlases created with data collected from autopsy tissue from the lung, heart, liver, kidney or brain[6,7,144–146] of patients who had succumbed to COVID-19 with atlases made using data from healthy and non-COVID-19 diseased reference tissues. These studies uncovered viral cell targets, dramatic changes in cell composition, pathological inflammatory and fibrotic circuits that partly mirrored those of other diseases, and failed and aberrant regeneration in different tissues — and also related these findings to genetic risk variants associated with severe COVID-19. Analysis of nasopharyngeal swabs from living patients with either mild, moderate or severe COVID-19 versus healthy individuals showed an impairment in local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19, which may underlie and precede disease[147]. Large-scale analysis of immune cells, including peripheral blood mononuclear cells (PBMCs)[148,149] or airway immune cells from living patients versus healthy reference cells, has shed light on myeloid and T cell states after SARS-CoV-2 infection[150] and has even suggested that antihypertensive treatments may 'prime' proinflammatory immune cells that are amplified upon infection[151].

Single-cell analyses have the potential to inform drug discovery as well as diagnosis and treatment in the clinic, as has been the case in the COVID-19 outbreak. For example, single-cell RNA-sequencing (scRNA-seq) of SARS-CoV-2-binding B cells from patients who had recently recovered COVID-19 (ref. [150]) identified high-quality neutralizing antibodies from memory and activated B cells[152]. ScRNA-seq of PBMCs from hospitalized patients helped to identify changes in cell composition[153] and gene expression along the course of disease progression[154]. In the context of the Pfizer–BioNTech mRNA vaccine BNT162b2 against SARS-CoV-2 (ref. [155]), a single-cell atlas of innate and adaptive immune cells collected longitudinally following first and second vaccinations identified a massive expansion of myeloid cells expressing interferon-stimulated genes after second immunization, but not natural infection — providing further insights into the efficacy of this new vaccine technology.

Diagnosis and treatment: single-cell insights to new clinical approaches

Towards a future of high-resolution cell and tissue diagnostics

Knowledge of all cell types in the body and their roles in disease should transform the future of common diagnostic tools, from single-cell assays such as complete blood count (CBC) and white blood cell count to histopathology. The healthy reference atlas, diseases atlases, and underlying lab and computational methods should allow for the development of new assays with higher resolution and broader molecular scope, as well as improved interpretation of results from individual patients (Fig. 1).

For the CBC — currently a census of a limited number of blood cell components that is used in a variety of diagnostic settings — we envision a future 'CBC 2.0,' a high-resolution portrait of the molecular profiles of nucleated blood cells, deployed in every disease. The rich and growing human reference now spans thousands of individuals and tens of millions of cells, with atlases of peripheral blood mononuclear cells from multiple diseases (such as melanoma[79], rheumatoid arthritis[80] and lupus[81]) and of immune cells in multiple tissues. Such a reference could form the basis for new diagnostic assays and for better interpretations, connecting the cell's profile in the periphery to those in healthy and disease tissue[79]. Excitingly, single-cell profiling of the blood immune cell landscape is beginning to inform our understanding of therapeutic responses and prognosis, including pioneering studies that have identified the blood correlates of the anti-PD1 response in tumors[79,82]. For histopathology, a workhorse of medicine, we envision conventional H&E staining being elevated to 'H&E 2.0,' in which single-cell and spatial profiling data are overlaid on standard tissue stains to unify genomic and histological analysis — either by direct lab assays or even by machine-learning algorithms trained on spatial data to predict molecular profiles from H&E stains[83]. As the use of spatial profiling (for genomics, epigenomics, transcriptomics and proteomics) in healthy[84–86] and disease[64,72,84,87,88] tissue[62,70,81,84,85] has grown, algorithms have been able to deconvolve low-resolution methods to single-cell resolution[89], project the spatial expression of genes that were not measured directly[89–93], and recover repeatable spatio-molecular features in tissue[70,94]. Given sufficient data, algorithms can also map molecular profiles and histology to each other, with the aim of predicting expression from histology[95], forming the basis of an H&E 2.0 approach.

Early studies are beginning to show the potential impact of such future assays, and how atlases provide the necessary tools to understand why therapeutics work — or don't work — in patients at the cell and tissue levels, predicting potential on-target toxicities, efficacy and mechanisms underlying intrinsic and acquired resistance. First, a healthy reference is invaluable in predicting the risk of on-target toxicities for both molecular and cellular therapies, on the basis of the cell types in which the therapeutic target is expressed. For example, a recent study has suggested that expression of CD19 by mural cells, vascular smooth muscle cells, and pericytes in the blood–brain barrier might explain neurotoxicity of CD19-targeting chimeric antigen receptor T cells[96]. Cross-species reference atlases for key models in safety assessment, such as rat and macaque[97], would be invaluable. For response and resistance in cancer, profiling malignant and immune cells in tumors, draining lymph nodes, or the periphery can help monitor response and provide insights into resistance, as shown, for example, in response to anti-PD-L1 therapy[82,98,99] or chemotherapy[100]. Although access to patient tissue may be more limiting in some cases, these approaches are as important in other diseases, such as IBD[29,42,51], rheumatoid arthritis[16,47], psoriasis[101], atopic dermatitis[52], and scleroderma[25].

High-resolution and massively parallel methods for drug discovery

For molecular drug discovery, reference atlases and single-cell and spatial genomics open the way to high-resolution phenotypic screens

for desired cell states by coupling the rich, complex and interpretable phenotypes of molecular profiles, which can be related to cells in patients, to the scale required in screening[102,103] (Fig. 1). Perturb-Seq screens – pooled genetic screens with single-cell genomics readouts – have characterized the impact on single-cell profiles of perturbations in large numbers of genes[102,104–107], non-coding variants associated with common complex disease[108], and coding variants in cancer[109] and developmental disorders[110,111], and can be performed in cell culture or co-culture, in organoids, or in animal models. Focused small-molecule screens with scRNA-seq readouts have also been conducted[112,113]. Moreover, machine-learning algorithms can increasingly be trained on such data to yield models that predict the impact of additional perturbations in one or more genes in the same cellular context or of the same perturbations in new biological contexts[114–116].

For regenerative medicine and cell therapy, single-cell atlases enhance our power to recover regenerative mechanisms in human tissue as therapeutic targets, develop better organoid models for drug discovery, and define better engineered cell therapies[117]. In each case, the comparison to reference atlases first helps define the desired target state, then helps screen for cells or organoids that achieve that state, and finally can help monitor the impact and state of the cellular therapy in the human patient. For example, when generating faithful human-derived models for regenerative medicine, healthy and disease reference atlases help compare model and human tissue, identify missing cellular components, and predict molecular mechanisms to improve the model[117], as has been shown for Parkinson's disease therapy[118], brain organoid models where autism-associated gene variants were introduced[111,119,120], gut enteroid cultures[121,122], thymic T cells[38], and organoid models of the endometrium[84] or intestines[123]. Moreover, for in vivo tissue reprogramming, reference atlases help infer differentiation mechanisms and assess whether a therapy has the desired effect, for example to characterize the regenerative capacity of overexpressing proneural transcription factors in Müller glia[124] or to map networks underpinning retinal regeneration[125]. Finally, for engineered cell therapy, Perturb-Seq methods help screen for perturbations that will yield therapeutically desirable cell states[126,127], and single-cell profiling helps characterize the resulting cell therapy before it is administered to patients and after administration in both common diseases[121] and T cell therapy in cancer[128–130].

Challenges for cell atlases in medicine

To realize the transformative potential of cell atlases in medicine, substantial challenges need to be overcome – technical, practical and fundamental (Fig. 1). First and foremost, we must ensure that cell atlases benefit all of humanity, by assembling healthy and disease atlases that reflect human diversity, from ancestry to geography, as well as involving diverse scientists from across the globe who are experts in these approaches. This has been a core aim of the Human Cell Atlas since its inception, and has been overseen by a dedicated equity working group[131,132]. For effective deployment in real-world settings, lab methods need to be sufficiently cost-effective and robust to empower screening and enable adoption, including in under-resourced areas. Connections between the lab and the clinic also need to be further enhanced, including building more biobank resources with rich metadata, large-scale profiling of samples from clinically annotated and diverse cohorts, and better experimental methods to tap into banked samples, especially formalin-fixed paraffin-embedded issues, which are still incompatible with many single-cell methods[133,134]. Among the key computational challenges are the need for open data that reflect human diversity for training computational models, while appropriately safeguarding patient privacy; methods to decode cellular dynamics from static snapshots; algorithms and platforms for efficient querying for genes, cell states and cell types of interest; and fast iterations between lab and computation to design faithful human-derived organoids and cells for screens and therapies.

Other challenges are more fundamental. First, while analysis of expression profiles yields suggestive associations, demonstrating the causative disease role of a gene, program or cell state requires direct interventions. Using single-cell and spatial genomics with genetic screens or in human genetic cohorts and clinical trials, along with causal inference, should help advance us from correlation to causation. Moreover, although cell atlases shed light on many changes as disease unfolds, they often focus on disease onset, rather than prognosis and progression. Longitudinal studies can address this challenge, but require long-term investment. More broadly, cell atlases on their own are an important tool in our arsenal, but not a silver bullet. We draw an analogy to the impact of the Human Genome Project, which did not 'solve' disease on its own, but instead laid critical groundwork for many areas of biomedicine[135].

Conclusion

As single-cell and spatial atlases continue to advance, they are transforming our understanding of different diseases at the cellular and tissue level, and are beginning to inform the development of diagnostics, drug discovery and novel treatment avenues. This has been impactful for new diseases like COVID-19, for long-standing ones such as cancer, and for rare and common complex diseases alike. Much of this progress has been driven by the rise of experimental technologies (Table 1) and computational algorithms that are applicable in studies at all stages of biomedicine, from understanding mechanisms to diagnosing and treating disease. As technological advances in sequencing, cell manipulation and spatial profiling are rapidly growing in scale and resolution (and dropping in cost)[136,137], they enable the collection of diverse reference atlases across genders, age, ancestry and demographics that are needed for clinical work. They also enable the sort of large-scale sampling within and across human patients that is required to understand and monitor disease, as well as screening experiments that are crucial to drug discovery. Together, these will help deliver the Human Cell Atlas mission: to form a reference map as a basis for understanding human health as well as diagnosing, monitoring, and treating disease.

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Competing interests

A.R. is a co-founder and equity holder of Celsius Therapeutics, an equity holder in Immunitas Therapeutics and, until 31 July 2020, was a scientific advisory board member of Thermo Fisher Scientific, Syros Pharmaceuticals, Asimov and Neogene Therapeutics. From 1 August 2020, A.R. is an employee of Genentech and has equity in Roche. A.R. is a named inventor on multiple patents related to single-cell and spatial genomics filed by or issued to the Broad Institute. J.E.R. and A.H. are employees of Genentech and have equity in Roche. In the past three years, S.A.T. has consulted or been a member of scientific advisory boards at Roche, Genentech, Biogen, GlaxoSmithKline, Qiagen and ForeSite Labs, and is an equity holder of Transition Bio.

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