Somatic mutations provide important and unique insights into the biology of complex diseases

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Somatic evolution of cells within the body is well known to lead to cancers. However, spread of somatic mutations within a tissue over time may also contribute to the pathogenesis of non-neoplastic diseases. Recent years have seen the publication of many studies aiming to characterize somatic evolution in healthy tissues. A logical next step is to extend such work to diseased conditions. As our understanding of the interplay between somatic mutations and non-neoplastic disease grows, opportunities for the joint study of germline and somatic variants will present themselves. Here, we present our thoughts on the utility of somatic mutations for understanding both the causes and consequences of common complex disease and the challenges that remain for the joint study of the soma and germline.

Somatic evolution in normal tissues

Four evolutionary forces operate in normal tissues

In classic evolutionary theory, species evolution is shaped by four evolutionary forces that affect allele frequencies in populations of individuals: mutagenesis, natural selection, genetic drift, and gene flow. These forces apply not only to individuals in a species but also to cells within the body. Imperfect replication and exposure to endogenous and exogenous mutagens cause all cells of the body to accumulate somatic mutations over time [1–5]. Mutations that occur during embryogenesis are present in a large fraction of cells postnatally and thus can result in the presentation of Mendelian diseases [6–8]. However, mutations continue to accumulate throughout life, and those arising postnatally are found only in the relatively small proportion of cells that are derived from the original mutant cell (clone, see Glossary), making them difficult to detect. Their frequency within a tissue is subject to constant change. Many are immediately lost by drift as the initial mutant cell is replaced by one of its neighbors. Others rise in frequency in the tissue either through random chance or by hitchhiking on one of the comparatively few who are favored by natural selection.

Positive selection dominates evolution in somatic tissues

Most somatic mutations are thought to be silent, with minimal phenotypic consequences. However, a small minority of mutations will affect the biology of the cell, either in a way that is selectively neutral or that subjects it to natural selection. In contrast to species evolution, which has been largely shaped by negative selection, the evolution of somatic cells is dominated by positive selection [9]. Mutations that confer selective advantage on a cell are termed driver mutations, and while much has been done to understand their role in cancers, relatively little is known about how they may impact other disease processes.

Highlights

- Every organ is a micromosaic of cellular clones carrying distinct somatic mutations that compete for space within the tissue but do not always increase cancer risk.
- Somatic evolution has the potential to affect the disease progress of common complex diseases. There is emerging evidence it can initiate disease, maintain disease once started, and possibly alleviate disease in some cases.
- The strength of selection of mutations in particular genes appears to vary between individuals. This is likely driven by differences in both lifestyle and environmental factors as well as germline backgrounds.
- Existing methods for studying somatic evolution in solid tissues do not scale sufficiently to allow for a well-powered genome-wide association study of mutation rates such that further developments are required.
**Somatic mutations in health and disease**

**Somatic evolution during normal aging**

Recent technological advances (Box 1) have enabled us to gain unprecedented insight into the somatic mutation landscape of normal polyclonal tissues [2–4,10–24]. These studies have revealed that cells found in histologically normal tissue frequently harbor one or more cancer driver mutations, and that the landscape of drivers and clonal expansions varies greatly between tissues (<5% of cells in colon, liver, and prostate carry drivers compared with >50% in the esophagus and endometrium of a 50-year-old individual). Furthermore, they suggest that parallel evolution, where independent clones carrying distinct mutations in the same genes grow in parallel within an organ, is common. The strength of selection for mutations in particular genes varies between individuals. For example, Lawson et al. studied somatic mutations in urothelium and found one patient with 35 distinct mutations in KDM6A and only two in ARID1A, while a second patient carried 20 different ARID1A mutations but only four KDM6A mutations [22]. Similar, but less pronounced, examples of parallel evolution have been described in other tissues. The observed driver preference is likely driven in part by the environment and in part by the germline background of the individual.

In extreme cases, parallel evolution can drive tissue remodeling to the degree that entire organs get repopulated with mutant clones [12,14,18,25,26]. For example, the entire esophagus of elderly individuals tends to become repopulated with clones carrying distinct mutations in the signaling molecule NOTCH1 [12,25] (Figure 1A). This near complete replacement of wild-type cells appears to be a normal feature of aging and has not been associated with any organismal-level phenotype. The process is accelerated by exposure to alcohol and smoking, common risk factors of esophageal cancer [25], but NOTCH1 mutations likely do not drive esophageal cancer development as once supposed, because they are more common in normal cells than in cancers.

**Clonal expansions in disease**

Chronic diseases often have profound consequences on the cellular constitution of affected tissues. The selection forces operating within a tissue are likely changed by disease, and mutations that maintain some small area of tissue. The disease then drives the expansion of a single clone. This mutation may push the cell down the path to becoming cancerous but need not do so.

**Box 1. Methods for the study of somatic mutations**

The major challenge when studying somatic evolution in non-neoplastic solid tissues is the highly polyclonal structure of the tissues. Mutations are typically not detected via bulk sequencing, as they are not found in sufficiently large fractions of cells to be distinguished from sequencing errors. Instead, most studies of somatic mutations use one of the following three technologies (Figure 1).

**Cell culturing:** the isolation and clonal expansion of single stem cells in culture is one way by which sufficient DNA can be obtained for sequencing [15,19,27,72,73]. The disadvantages of this approach are that not all cell types can be expanded in tissue culture, and that spatial information between stem cells is lost as the tissue is dissociated. Furthermore, cells accrue mutations during culturing, and culture conditions may exert selective forces that bias downstream analyses. Culturing has the advantage, however, that cells from clones found to carry mutations of interest can be retained and subjected to experimental functional assays [57].

**Laser capture microdissection:** this method involves using a laser to cut small groups of cells from histological sections that can then be sequenced. It has the advantage that the spatial relationships between all groups are known, which gives information about clonal relationships between cells in the sample millimeters or centimeters apart as well as locally active mutational processes [15,16,22,28]. The method relies on the ability to identify at least semiclonal populations of a few hundred cells in the tissue and is not feasible for highly polyclonal tissues [74].

**Single-cell sequencing:** methods have been developed to call mutations both from single-cell DNA (scDNA) and single-cell RNA (scRNA) datasets [75–77]. Single-cell technologies have the advantage that mutations can be called even in highly polyclonal tissue, such as postmitotic neurons [2,23]. These methods, however, are hampered by a high error rate. Single-cell studies typically rely on multiple displacement amplification to generate sufficient DNA for sequencing. This process is associated with a high rate of artificial chimeric DNA molecules, which results in a very high fraction of false-positive mutation calls [75,76].
that were neutral under normal conditions may become advantageous in disease conditions. Cells that harbor mutations, which enable them to withstand the disease environment while their neighbors perish, can quickly grow to a high frequency in the tissue through a series of bottleneck–expansion cycles (Figure 1B), as seen in inflammatory bowel disease [26–28] and liver disease [16,17]. Disease can also be associated with accelerated mutagenesis and exposure to novel mutagens and affect genetic drift by altering cell proliferation. Understanding these processes is an important part of understanding the biology of the disease and vital if we are to establish the causal directions of the mutations.

Independent of causality, for somatic mutations to have a significant effect on the phenotype of an organism, they must first reach some minimal prevalence within a tissue, a threshold that likely varies between mutations, tissues, and phenotypes. Mutated cells may reach high frequency in a tissue either through the large-scale expansion of a single clone or through parallel evolution of multiple clones, each carrying a distinct mutation in the same gene or pathway.
Somatic mutations as drivers of disease

One of the best characterized examples of a single growing clone leading to complex disease is the relationship between clonal hematopoiesis and cardiovascular disease. Between 10% and 20% of individuals over the age of 70 harbor a mutant clone that accounts for >4% of their blood cells. These clonal expansions can occur without a detectable driver mutation [29] or can be driven by copy number alterations [30–32] or by point mutations in specific genes, especially DNMT3A, TET2, ASXL1, and JAK2 [33–35]. All forms of clonal hematopoiesis are associated with increased risk of developing a hematological malignancy, but the point mutations are additionally associated with many cardiovascular outcomes, including ischemic stroke, atherosclerosis, myocardial infarction, and more [30], with a similar hazard ratio to common risk factors such as high blood pressure and smoking (reviewed in [36]).

Mutations in TET2, which encodes a chromatin modifier that represses the transcription of pro-inflammatory molecules, have been best characterized. They result in increased expression of...
various cytokines and chemokines in monocytes and macrophages, including interleukin-6 (IL-6), IL-1β, and members of the CXC family. This drives a higher expression of endothelial adhesion molecules, leading to increased leukocyte recruitment to the aortic site. Macrophage uptake of lipids and cholesterol crystals ultimately leads to plaque formation and atherosclerosis [37,38] (Figure 1C). People with TET2-driven clonal hematopoiesis who also carry the germline variant IL-6R p.Asp358Ala, which impairs the receptor signaling [39], are at increased risk of cardiovascular disease [40]. These findings suggest that IL-6 pathway antagonists might decrease the risk of cardiovascular disease in general and especially in people with large TET2-mutant clonal hematopoiesis. This example highlights the utility of profiling somatic mutations to identify potential drug targets for diseases other than cancer and to aid precision medicine.

Epidemiological studies have linked clonal hematopoiesis (and the somatic loss of ChrY in blood) with a number of other outcomes, including ovarian aging [41], Alzheimer’s disease [42], age-related macular degeneration [43], and more, but whether these are due to direct effects of clonally expanded leukocytes or confounding factors, such as shared cell cycle regulation mechanisms, remains uncertain. Recent studies in solid tissues suggest that somatic mutations might play a role in epilepsy [44,45], autism [46], endometriosis [14], cirrhosis [17], and more [47]. With the possible exception of epilepsy, where functional follow-up has been carried out in a mouse model [44,45], more data are required to confirm the direction of effect of these mutations (see more about causal inference later). We present a case study of inflammatory bowel disease (IBD) in Box 2, which encapsulates many of the principles discussed generally in this paper.

Somatic mutations as nature’s gene therapy

In some cases, somatic mutations may confer upon cells resistance to the effects of disease. The expansion of disease-resistant cells within a tissue could potentially restore some of the tissue function. The existence of mutations restorative to tissue function has been proposed in chronic liver disease [17] but remains a theoretical prediction for most other complex diseases. However, they have been reported in several germline conditions in which the molecular effects of pathogenic germline variants are rescued by somatic variants conferring selective advantage on the revertant cells [48]. Those observations also further underline the importance of parallel evolution. Multiple revertant clones evolving in parallel have, for example, been reported in patients with Wiskott–Aldrich syndrome [49], ichthyosis [50,51], and in various types of genodermatoses [52–56] (Figure 1D).

We posit that identifying and pharmacologically mimicking mutations driving the positive selection of disease-resistant clones could restore tissue homeostasis and alleviate disease symptoms. For such efforts to be successful, it will be important to establish the causal relationship between variant and disease and rule out disease-expansion feedback loops, where the mutations that facilitate cell survival also contribute to the disease process.

Establishing the causal relationship between somatic mutations and disease

If somatic mutations are to inform complex disease drug target identification, then the causal relationship between variant and disease must be established. Mouse models have been useful in the studies of clonal hematopoiesis, epilepsy, ichthyosis, and IBD [37,38,44,45,57–59], but evidence of causation in humans is still outstanding.

Untangling cause and correlation in humans

Mendelian randomization (MR) has become widely used in the human genetics field for causal inference in epidemiological studies [60,61]. Assuming that mutations in a given gene drive clonal
expansions in a given tissue causing disease, then any variable that influences the propensity of clonal expansion in that tissue should also be associated with the disease. A causal relationship between the clonal expansion and the disease can be inferred if an ‘instrument’ variable reliably associated with clonal expansion in a known direction, can be identified. Genetic variants are excellent choices for such instruments because associations between germline variants and human traits represent causal relationships since alleles segregate randomly during meiosis, and reverse causation is not possible (disease cannot ‘cause’ a germline variant). MR, and specifically bidirectional MR, could theoretically be applied to distinguish somatic variants with a causal effect on complex disease from those that are a consequence of disease. If the expansion of clones carrying mutations in a specific gene causes a disease, then genetic variants associated with the propensity for clonal growth will also be associated with the disease (assuming that this association occurs only through the effect on clonal growth).
In addition to the conventional assumptions and limitations of MR, covered elsewhere [60,61], the assumption of a single causal direction merits special consideration when studying somatic evolution. Disease–expansion feedback loops, where disease drives clonal growth that in turn perpetuates the disease and so on, have been proposed for clonal hematopoiesis and atherosclerosis [62] and may also exist between IBD and IL-17 mutant clones (Box 2). It has been suggested that these can be modeled in a structural equation modeling framework [63], but, as far as we are aware, these methods await development. Furthermore, care must be taken when interpreting associations between germline variants and somatic mutation frequencies. Cis-associations need not represent causal relationships because germline haplotypes can be in linkage disequilibrium with fragile sites of the genome and other mutational hotspots.

Building germline genetic maps of somatic evolution
To utilize the power of MR for causal inference, it is essential that we build robust genetic maps of somatic evolution in health and disease. The availability of hundreds of thousands of blood samples from biobanks has enabled the discovery of 156 germline variants associated with somatic loss of chromosome Y in men [64–66] and of 10–20 variants associated with the likelihood of clonal hematopoiesis [29,30,67,68]. The variants associated with ChrY loss have odds ratios (OR) ranging from 1.03 to 2.02 [66], and similar effects are observed for the common variants associated with clonal hematopoiesis [29,30,67,68]. Most fall within noncoding regions of the genome. These observations suggest that genomic instability and clonal evolution phenotypes are complex in nature and have a genetic architecture similar to that of other quantitative traits. Rare chromosomal alterations and loss-of-heterozygosity events (frequency <0.05%) have also been reported that have much larger effects on clonal hematopoiesis (ORs = 18–698) [30–32]. Most variants with large effects on clonal hematopoiesis are copy number-neutral loss-of-heterozygosity events, where a chromosomal segment containing an allele that promotes blood cell proliferation is made homozygous in the cell.

Interactions between germline variants and known somatic drivers of disease have been most systematically studied in the context of cancer. A study of The Cancer Genome Atlas (TCGA) dataset [69], which was only powered to detect large effects (1.8–3-fold increase in mutation burden, depending on the frequency with which genes are mutated in cancers), reported 17 associations between common germline variants and the frequency of somatic mutations in known cancer genes. The effect sizes reported ranges from 1.8- to 14.8-fold increases in mutation frequency. It is possible that germline effects on selection pressure are higher in solid tissues than in blood, where the admixture of cells is greatest. Tissue architecture and driver prevalence can influence clonal spread. For example, the glandular structure of the colon seems to curb clonal spread, [15] while in the flat structure of the esophagus where the density of driver mutations is high, the spread of any one clone is constrained by its collision with neighbors of similar fitness [70]. How such variables influence germline effect sizes is unknown. It is also possible that the effects of germline variants are larger in cancers than in the evolution of non-neoplastic tissues.

A two-tiered approach for detecting cis-associations
For genome-wide association study (GWAS) of somatic evolution in solid tissues, obtaining and processing sufficient samples with the methods presented in Box 1 would be extremely expensive and labor intensive. Furthermore, important clones could still be missed even after processing multiple samples per individual. This adds uncertainty to the phenotype and reduces power to detect associations between germline variants and somatic mutation frequencies. To maximize power in the short term, a two-tier study design could be adopted where a genome-wide screen is first undertaken to identify genes under positive selection, followed by a search for cis-effects.
on clonal evolution at germline variants near the positively selected genes. This is similar to a common design of expression quantitative trait locus (eQTL) studies, where a list of genes expressed in the tissue of interest is first compiled, followed by testing variants for cis-effects on each expressed gene. While many thousands of expressed genes are included in a typical eQTL study, the multiple testing burden would be much lower when searching for cis-effects on somatic evolution due to the much smaller number of genes under positive selection in a tissue. This approach assumes that cis-effects play a role in clonal evolution, an assertion supported by recent evidence that germline variants in or near JAK2 and TET2 are associated with clonal hematopoiesis [68]. In IBD, NFKBI2 is both positively selected in inflamed epithelial tissue and a likely causal gene in a GWAS locus for the disease (Box 2), although it is not clear if the IBD-associated germline variant affects selection of NFKBI2-mutant cells.

While cis-variants clearly play some role in shaping positive selection, these may only represent a small fraction of all associations. Most variants associated with clonal hematopoiesis lie outside of known driver genes, and variants associated with somatic ChrY loss are scattered all across the genome. Furthermore, of the 17 associations discovered in the TCGA dataset mentioned earlier, the leading variant was never within 1 Mb of the gene whose mutation burden it was associated with [69]. In the short term at least, other forms of restricted hypothesis testing are likely required to identify trans-effects on somatic evolution in solid tissues. Testing only variants known to drive cancers in these tissues or variants associated with known proxies of genome instability seem reasonable first options. One example of the latter may be variants associated with somatic loss of ChrY [46], although it is not clear if these associate with genome instability or promote the selection of cells that have lost ChrY.

Population differences in somatic evolution
There is evidence that somatic evolution varies across different ancestries. In a study of normal skin from just four individuals, the one donor of South Asian ancestry seemed to exhibit a different evolutionary landscape from the other three [10]. Similarly, the selection of NFKB1Z--, ZC3H12A-, and PIGR-mutant clones shows more pronounced in IBD patients of Japanese ancestry than Europeans [28,28], as discussed in Box 2. Furthermore, white Europeans are nearly twice as likely as Hispanics and East Asians to develop clonal hematopoiesis after adjusting for age [68]. European individuals also have a two- to sixfold increase in the mutation rate of specific sites linked with clonal hematopoiesis compared with Japanese individuals, a finding that helps explain the different rates of B cell and T cell cancers in these populations [31]. While it is unclear to what extent these population-specific differences are due to environmental or germline differences, they highlight the need to study somatic evolution in diverse populations.

Concluding remarks
We have begun to build our understanding of somatic evolution in healthy tissues. Now is the time to expand that study to diseased tissues to understand both how diseases change the evolutionary landscape of tissues and the potential role somatic mutations play in disease onset and progression (see Outstanding questions). The studies published to date are too small to enable joint study of germline and somatic variants for all tissues except for blood. The biggest and the most important challenge for the integration of germline and somatic variants is therefore the scaling up of methods for somatic mutation detection. This could happen through the development of high-throughput noninvasive sampling methods and/or by development of methods to avoid formalin-associated artifacts, which would enable the repurposing of existing clinical biobanks for research. Recently published methods for accurate calling of mutations from single DNA molecules [5,71] represent exciting advances and may facilitate larger-scale projects. Once we can accurately ascertain the mutation landscape of tissues across hundreds or thousands of individuals,
we can unlock the unique potential of somatic mutations to understand disease biology and identify novel drug target candidates.

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Declaration of interests

C.A.A. has received consultancy fees from Genomics PLC and BridgeBio Inc. S.O. holds a small number of shares in 10x Genomics, Pacific Biosciences, and Twist Bioscience Corp.

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