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Exploring intermediate cell states through the lens of single cells

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Highlights

- Intermediate cell states exist between well-defined cell

types" in many tissues.

- Intermediate states regulate reversible transitions between cell types.
- Single-cell transcriptomic data have changed our understanding of intermediate cell states, leading to their gain or loss.
- Functional characterization of intermediate states is provided along with description of how mathematical models are used to interrogate these functions.
- Means to predict intermediate states from single-cell data are provided.

Abstract

As our catalog of cell states expands, appropriate characterization of these states

and the transitions between them is crucial. Here we discuss the roles of intermediate cell states (ICSs) in this growing collection. We begin with definitions and discuss evidence for the existence of ICSs and their relevance in various tissues. We then provide a list of possible functions for ICSs with examples. Finally, we describe means by which ICSs and their functional roles can be identified from single-cell data or predicted from models.

Previous Next

Keywords

Intermediate state; Transition state; Cell plasticity; Hybrid cell type; EMT; Cell differentiation; Cell lineage; Multistability

Introduction

Studying single cells in high resolution has led to many advances, including new ways to characterize and understand cell states. These

can be persistent and accompanied by well-defined functions – commonly referred to as cell types – or they might occupy less well-characterized roles in an atlas of cells (see the Human Cell Atlas project [1]). These latter cell states are referred to as *intermediate, hybrid, or transition states* in various contexts. Single-cell studies have advanced our ability to probe these states, but require new computational methods and theoretical models for analysis, as they are typically high dimensional (tens of thousands of genes measured in thousands of cells). With rapidly improving experimental techniques, more complex landscapes of cell states will be investigated and revealed, making development of appropriate tools even more important. Characterizing the heterogeneity present within and between cell states is crucial to understanding them and defining their boundaries; here models accelerate progress, as cell states can be defined as attractors on a potential landscape. Below we will discuss the role of noise in cell states: how biology both accounts for it and exploits it, in various contexts.

Intermediate cell states (ICSs) can be defined in terms of cellular phenotype, i.e. the quantifiable characteristics of a cell, which include gene expression, protein abundances, post-translational modifications, and cell morphology. We consider any state that lies between two traditionally defined cell types (i.e. cell states that have accompanying functions) to be *intermediate* (Figure 1A) and we refer to a generic intermediate cell state as an ICS of Type 0. These cell types may be distinguished from each other by either quantitative or qualitative measurement. While heterogeneity *within* a given cell state may also be functionally relevant, we limit our discussion here to cell states with distinct functions.

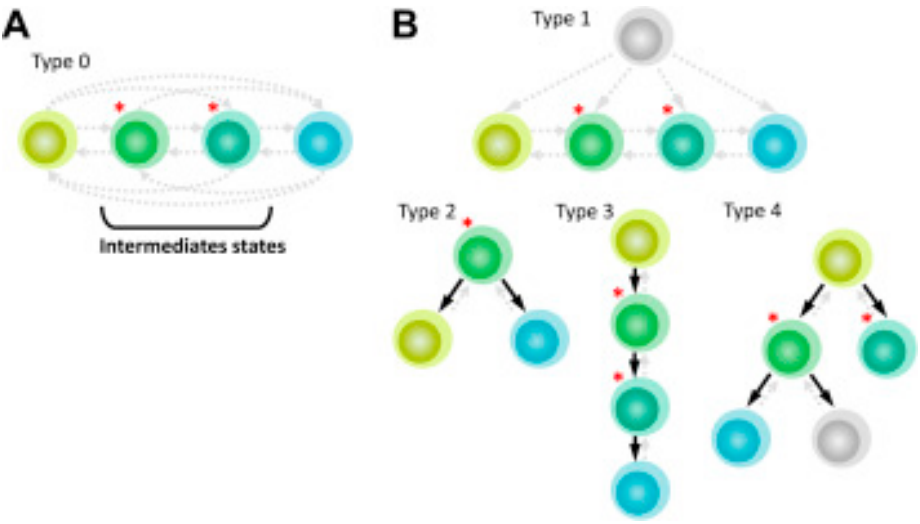

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Figure 1. **Identities of intermediate cell states (ICSs).** (A) An ICS (green, asterisk) refers to any phenotypic state lying between traditionally defined cell types (yellow or blue); generic ICSs are referred to as Type 0. (B) ICSs can facilitate cell state transitions in many ways, occupying the same (Type 1) or distinct (Types 2&3) hierarchical levels as other cell states. Complex lineage transitions can be mediated by ICSs (Type 4).

ICSs become particularly important when they mediate transitions, which can have distinct meanings in different contexts (Figure 1B). ICSs can be 'lineage siblings' (Type 1), i.e. share a hierarchical level with terminal states. Other ICSs occupy distinct hierarchical levels from terminal states and potentially also between themselves (Types 2 and 3). ICSs can also exhibit more complex lineage relationships (Type 4).

In the following discussion, we seek to characterize ICSs and discuss how they may be

predicted conceptually, either from models or data; we do not however provide specific methods with which to identify ICSs. For comparative purposes, we focus on three biological systems and the roles of ICSs in each. These are: the epithelial-to-mesenchymal transition (EMT); hematopoietic progenitor cell differentiation; and $CD4^+$ T cell lineage specification. The ICSs in these systems can be classified with the definitions above (Figure 1B) (EMT: Types 2 & 3; Hematopoietic stem/progenitor cell states: Types 2–4; $CD4^+$ T cells: Type 1).

The existence of intermediate states

EMT. Epithelial and mesenchymal cells are distinguished by cellular function, morphology, migratory behavior and transcriptional programs. During embryonic development, epithelial cells undergo a transition to a mesenchymal state, a process known as epithelial–mesenchymal transition (EMT). This transition is associated with the loss of cell–cell junctions and cell polarity, and the acquisition of migratory and invasive

properties. The EMT is reversible: mesenchymal-to-epithelial transition (MET) may occur in development and other physiological conditions, and is important for the morphogenesis of internal organs 2, 3. The EMT-MET system thus appears to be highly dynamic in response to either intrinsic signals or the microenvironment. Complex signaling and transcriptional networks 2, 4 control this plasticity of cellular phenotypes.

Initial characterization of EMT indicated a binary decision between E (epithelial) and M (mesenchymal) states. While the notion of a direct transition is useful and parsimonious, it cannot explain key observations regarding partial phenotypes exhibiting both E and M characteristics, during morphogenesis or cancer progression. These data have stimulated mathematical modeling and quantitative experimentation to characterize partial EMT. Modeling studies have revealed that complex EMT regulatory networks govern the existence and stability of multiple ICSs **5, *6, 7, *8, 9, for example two EMT ICSs displaying distinct differentiation propensities

[5]. Experiments have found evidence for these states in the mammary epithelium, both naturally and signal-induced [5], in agreement with experiments showing multiple ICSs in similar systems 10, 11, 12, 13. These systems approaches have led to a new paradigm for EMT involving multiple transitional stages [14]. Intermediate EMT states can be classified as Type 3 in Figure 1B, where they serve as 'waypoints' assisting with cellular plasticity, but recent association of EMT ICSs with stemness leads to the hypothesis that these states may be more undifferentiated (Type 2) [15]. The differential stability and dynamic behaviors of these intermediate may be critical to morphogenesis, wound healing and disease progression [14].

Hematopoietic progenitor cells. Hematopoiesis proceeds by an archetypical stem cell process: a rare cell population with the capacity to self-renew indefinitely gives rise to the many differentiated cell types of the blood system. Characterization of the differentiation paths traveled by hematopoietic stem cells (HSCs) led to the

construction of a hematopoietic lineage tree consisting of multiple lineage-restricted progenitor cell populations controlling successive bifurcations (Type 4 in Figure 1B), leading eventually to the various distinct and specialized cell lineages [16]. Whereas some progenitor cell populations represent cell types, others may be ICSs; our characterization of these is incomplete. Furthermore, each of these lineages may still contain (unipotent) progenitor cells and have capacity for further specification and complex cell fate dynamics involving ICSs (e.g. the $CD4^+$ T cell lineage). Experiments mostly based on cell surface marker expression via flow cytometry led to this view of hematopoiesis; but differentiation culture experiments were performed at a population level and thus unable to resolve single progenitor cell fate decisions. Modeling studies have been able to delineate the landscapes and cell states of stem and progenitor populations, as well as the timings of cell fate decisions and some of the regulatory networks that control these decisions 17, 18, 19, 20, 21, 22. In the case of

multiple steady states, generalized stability analysis can map out the global stability properties of the landscape and thus define the basins of attraction in parameter space [23]; progenitor cell states tend to lie in shallower wells than stem or differentiated cell states [24]. These studies have, until recently, focused for the most part on population dynamics. Significant plasticity/heterogeneity within progenitor cell populations has been hinted at in the past [25], but only recently have we become able to probe these phenomena in detail.

Single-cell analysis and models have led to dramatic changes in our characterization and understanding of cell states during hematopoietic differentiation. Previously well-defined intermediate progenitor states were revealed to be – rather than a single population – mixtures of heterogeneous cell populations 26, 27. Thus rather than a bifurcating tree-like lineage, a fan-like lineage has been proposed with fewer intermediate progenitor states and earlier lineage restriction (Figure 1B Type 1). Single-cell differentiation assays provide functional

differentiation assays provide functional means to test the composition of these controversial states, and have found that, in agreement with gene expression data, the megakaryocytic-erythrocytic progenitor population is not in fact composed of bipotent progenitor cells, but rather consists of lineage-restricted erythroid or megakaryocyte progenitors, along with cells exhibiting high plasticity (see Function 4) [28]. In addition, new ICSs have emerged, for example a "multi-lineage" state associated with the monocytic-granulocytic cell fate choice that might act as a primed state in which cells can become "trapped" if they do not receive the appropriate transcriptional cues [29].

If we consider the landscape of hematopoietic differentiation, these new data suggest we must go beyond Waddington's classical bifurcating valleys [30]; instead, saddle points might lead to three or more new cell states [31]. This additional complexity presents both a challenge and an opportunity for modelers. These results also have implications for non-hematopoietic tissues such as the skin, which have simpler differentiation trajectories

have simpler differentiation trajectories (fewer – or perhaps no – bifurcations), but still pass through intermediate progenitor states en route to terminal differentiation. As we begin to interrogate these lineages in greater detail [32], our understanding of the existence and nature of ICSs may again be subject to change.

CD4$^+$T cells. CD4$^+$ T cells play an essential role in the adaptive immune response, exhibiting a remarkable diversity of transcriptional programs and functions. They coordinate an immune response by releasing cytokines specific to the immune activity and to their own identity. Differentiation of CD4$^+$ T cells is triggered by pathogenic challenges to an organism, which are followed by antigen-presentation to the naïve (undifferentiated) CD4$^+$ T cells, influenced by surrounding cytokines [33]. These antigen and cytokine signals determine the fates of the CD4$^+$ T cells.

Previous experimental and modeling studies focused on signaling networks controlling fate determination of CD4$^+$ T cells, with the underlying assumption that cells adopt

discrete and mutually exclusive transcription programs upon differentiation 34, 35, 36, 37, 38. However, mutually exclusive differentiation has been challenged by numerous observations in the past decade: multiple studies have found intermediate (hybrid/double-positive) $CD4^+$ T cells, which are generated together with the 'terminal' cells and stably maintained (Type 1, Figure 1B). For example, cells expressing both RORγt (master regulator of Th17) and Foxp3 (master regulator of Treg) exist in human and mouse, and can be stably maintained in culture under non-polarizing conditions 39, 40, 41. Other ICSs, e.g. Th1—Th2 and Th1—Th17 cells, can be found in various physiologically relevant conditions 42, 43, 44, 45, 46, 47. The formation of these ICSs can be explained by modeling the core transcriptional networks 48, 49, *50. In addition to the identification of cells that express key factors of two lineages, stable cellular states with varying lineage-defining factors have been reported for $CD4^+$ T cells 51, 52. Eizenberg-Magar et al. found that $CD4^+$ T cells combine cytokine signals and choose

cells combine cytokine signals and choose their fates in a linear continuum in vitro, although the stability of these states in vivo has not been examined [52]. Th1 cells have been shown to have stable quantitative memory in terms of the cytokine production rates [51]. These observations suggest that many possible cellular states exist between the extrema of the $CD4^+$ T cell phenotypic spectrum. The stability of some of these ICSs has been demonstrated, however the fates of $CD4^+$ T cells are plastic, and transitions between states can occur during immune responses 53, 54, 55, 56. The relative contributions of cells undergoing lineage transitions between ICSs are less clear.

The three examples discussed above are among many biological systems where ICSs exist. In fact, the ICS may appear ubiquitously in developmental processes involving gradual cell fate determination 57, 58, 59, 60. In mature systems, ICSs may appear between cell types that possess sufficient plasticity, including cancer cells, and those systems which involve dynamics among multiple subpopulations 61, *62.

subpopulations 61; *62.

The role of noise in intermediate states

The plastic nature of epithelial and mesenchymal cell states (along with ICSs) highlights the importance of studying the dynamics of this system in fine detail. Intercellular signaling molecules such as TGF-β and BMP influence EMT-MET transitions, but it is not clear how intracellular noise influences the transition dynamics. Stochastic simulations suggest that ICSs have different differentiation propensities, driven by fluctuations in gene expression, and that noise can trigger transitions into an ICS from a terminal state [5]. In addition, an ICS allows noise-induced switching more easily, such as the transition from a main state to an ICS, then to another main state. Such noise-induced switching is beneficial in cell fate specification 63, 64.

Stochasticity plays a central role in hematopoietic progenitor cell dynamics, and new states have been gained and lost

according to different measurement and analysis techniques 26, **29, 65. Mathematical models have been used to study stochastic hematopoietic dynamics in various ways 66, 67, 68, but have yet to describe single-cell fate decision dynamics. Experimentally, techniques are improving to observe cell-to-cell heterogeneity [28], highlighting the importance of these effects during hematopoietic differentiation.

Stochastic fate choices for multiple $CD4^+$ T cell lineages and corresponding ICSs have been observed and modeled 41, 48, 49, *50. Stochastic cytokine production has been reported in transitioning Th1—Th2 intermediate cells [69], however, differentiated Th1 cells have stable states in terms of their levels of cytokine production, and stochastic switching between the quantitative states is very limited [51]. Whether stochasticity contributes significantly to the long-term behavior of intermediate phenotypes remains an open question.

Possible functions of intermediate states

Here we discuss known or predicted functions of ICSs under five headings, and give examples for each. We consider two generic cell types (A and B) and the transitions that occur between them, which could be due to lineage dynamics or to metaplasticity.

1. The ICS controls bidirectional transitions between cell types. If cell types A and B are separated by a gap in phenotypic space, then an ICS might enable a transition from A to B. Or, if the transition A→B exists, but the transition B→A does not, an ICS might enable this reverse transition. An ICS could also have a negative effect on the transition A→B, by either reducing the rate or halting the transition completely, thus acting as a sink.

In EMT, using landscape theory to characterize the kinetic paths of a three-state EMT system [70], we found that transitioning through an ICS may be required when an EMT-inducing signal is not sufficient to convert E to M

directly. In hematopoiesis, the existence of ICSs that were previously thought to drive bifurcations during differentiation has been challenged 26, 27, leading to new roles for ICSs with greater lineage bias but reduced multipotency (perhaps precluding these states from performing function 4 below) [29]. Since new roles for ICSs in facilitating differentiation have yet to be carefully defined (a challenge exacerbated by the speed with which our understanding of the hematopoietic landscape is changing 59, 71, 72), much work remains to be done; here modeling studies will likely play a crucial role. In culture or pathogenic settings, dedifferentiation can occur; such reversibility is also widespread for metastatic transitions: the role of ICSs in reversible (or reverse) transitions is likely important but remains to be well defined.

2. The ICS exhibits a hybrid phenotype. For cell types A and B with distinct functions, an ICS can display a hybrid phenotype containing characteristics of phenotype A and phenotype B. There could exist a transition A→B, or B→A, or there could be no transition.

Several studies have found that intermediate $CD4^+$ T cells produce cytokines of mixed lineage signatures and functions 40, 43, 45, and the dual-function of Th1—Th2 intermediate cells in limiting immunopathologic inflammation [47]. It has been proposed that the ICSs can serve as 'moderators' that help to avoid damage from extreme immune responses [73]. It has been suggested that intermediate EMT cells may exhibit a hybrid function with regards to collective migration; a key feature of invasive cancer cells requiring both cell-to-cell contact and the ability to migrate. As for hematopoiesis, in terms of the *stemness* axis, progenitor ICSs are – at least in part – by definition hybrid states, exhibiting mixed stem-like and differentiated cell characteristics 28, **29.

3. The ICS controls size fluctuations of cell populations. An ICS between cell types A and B can regulate the variance of cell types A and B. This regulation might act to stabilize the cell populations via ICS transitions, or the ICS can be used by the system to increase the

variance without changing the mean.

Models have predicted that multiple ICSs can facilitate the attenuation of fluctuating cell populations [74]. By absorbing some of the noise, these additional states serve as 'buffers' against environmental fluctuations, thereby preventing imbalances of cells in terminal states. These homeostatic properties could be hijacked by cancer; their misregulation leading to increased invasiveness. Recent experiments have shown that key genes – which may regulate ICSs and induce transitions – control fluctuations without affecting the mean of the gene expression state [75]. The level of temporal fluctuations is determined by a critical quantity called the Signed Activation Time 76, 77, which may be regulated by ICSs. Increasing cell heterogeneity, made possible by ICSs, can also enable faster regeneration and reduce the variability in desired cell populations [78].

4. The ICS expands the reach of a cell type. In various cell transition processes, including differentiation,

reprogramming/dedifferentiation, or direct reprogramming, the number of cell states accessible to a cell at any given time can change. The ICS can act to change this cell type "accessibility", which can, in different contexts, be thought of as potency, stemness, or potential to broadcast information [79]. Increasing accessibility implies greater potency/stemness, while decreasing accessibility may correspond to/result from differentiation.

The bipotent characteristics of intermediate EMT states have led to suggestions that these states have higher stemness and invasiveness than terminal states. This association of the ICS with stemness has been found in cancer cell lines, and the signature genes associated with the intermediate state are correlated with poor cancer prognosis [15]. However, the functional role of multiple ICSs under normal physiological conditions is less clear. In hematopoiesis, controlling cell state accessibility during transitions is closely linked to the traditional functions of progenitor cell states, however (as discussed

above) some of these functions have recently been called into question. The landscape of hematopoietic differentiation, which leads to many diverse cell types, must be controlled at points of lineage restriction/fate choice. Mutual inhibition (toggle-switch) models can control bifurcations 19, 22, 66, but if more complex decisions occur (see Ref. [29]), larger transcriptional networks may be required **5, 31.

5. The ICS as a cell ledger. The ICS can be used to record information regarding cell dynamics, for example acting as a checkpoint during differentiation, requiring a certain threshold to be met by counting progenitor cells before differentiation proceeds.

For example, mesenchymal stem cell states exhibit memory in response to mechanical stimuli, thus providing a means to record cell counts [80]. In early T cell development, multiple intermediate stages may serve as checkpoints that ensure proper transcriptional programs and sufficient cell expansion are achieved 59, 81. In particular, DN1 (the

earliest intermediate stage of T cell development in thymus) cells need to undergo multiple cell divisions before progress to the DN2 stage [82]. This regulation of differentiation competence by cell expansion is critical for T-cell homeostasis, and it could represent a more general strategy for maintaining cell populations through ICSs.

Modeling and computational approaches to find intermediate states

In many cases, prior knowledge of the gene regulatory networks of a biological system provides a good starting point for the identification of ICSs. Typically, models describe interactions among genes, protein abundances, post-translational modifications, or chromatin states, and are characterized by a system of equations (discrete or continuous). The challenge then becomes finding and classifying *all* the steady state solutions of the system that correspond to cell states [83]. Locations (in state space) and stability properties (e.g. stable, meta-stable, unstable)

are critical quantities to consider for ICSs [84].

One minimal condition for finding ICSs is the existence of five distinct steady state solutions, three of which need to be stable [49]. Network topologies that give rise to such multistability typically contain a core mutual inhibitory circuit with additional positive feedback loops on one or more genes. For systems of a small number of genes, nullclines and numerical bifurcation analysis are applicable for analysis **5, *50, while for systems of a large number of genes, more sophisticated computational tools are required. Interestingly, in some cases, stable ICSs may emerge only in a stochastic model of the system [85]. Exploration of stochastic dynamical systems requires effective numerical methods that can deal with temporal stiffness in the rate constants 86, 87, 88.

When the cell state space is defined in high dimensions (e.g. by expression of many genes), statistical methods are needed to identify ICSs. Dimensionality reduction and

hierarchical clustering are common strategies for quantifying the distances among cells and defining the state space in lower dimensions 10, 89. Additional metrics can be used to define a linear spectrum of phenotypes so that the possible states in the spectrum can be scored quantitatively 10, 90.

Single-cell analysis approaches to find intermediate states

Single-cell transcriptomic data provide a flexible and unbiased way to search for ICSs in gene expression state space. For example, single-cell analysis has shown that metastatic mammary epithelial cells exhibit strong phenotypic variations [91], and indicates the involvement of one or more ICSs, but their relationships with stem cell subpopulations and EMT/MET need to be further analyzed. Bifurcation of Th1 and Tfh cells during *Plasmodium* infection has been discovered via single-cell sequencing [92], and multiple ICSs during $CD4^+$ T cell differentiation have been suggested [93], however, these studies did not address a central question: how are mature

$CD4^+$ T cell ICSs distributed on a gene expression landscape? Future single-cell analysis will help to resolve this picture of mixed phenotype states 94, 95. Single-cell analysis of hematopoietic progenitors has led to dramatic changes in the understanding of the cell state landscape as discussed above, with corrections made to our previous (false) perceptions of some progenitor cell states 26, 27, 28, and the discovery of others [29].

The existence of an ICS from single-cell data can be predicted by analysis methods. In Figure 2A, a hypothetical low-dimensional projection of single cell data (e.g. via RNA sequencing) is shown, colored by subpopulation identity. These subpopulations could be determined by biological markers or predicted by clustering [96] or energy-landscape based methods [97]. Three possible means to identify ICSs from such a dataset are shown (labels (i)-(iii)). Cluster C2, of class (i), is defined by its distinctness in pseudotime (Figure 2B), suggestive of a state involved in phenotype transitions. Class (ii) (Cluster C5) appears as a distinct subpopulation between

other subpopulations, and may also represent an intermediate state. Finally, type (iii) represents a mixture of subpopulations (C6 and C7), which could also predict an ICS.

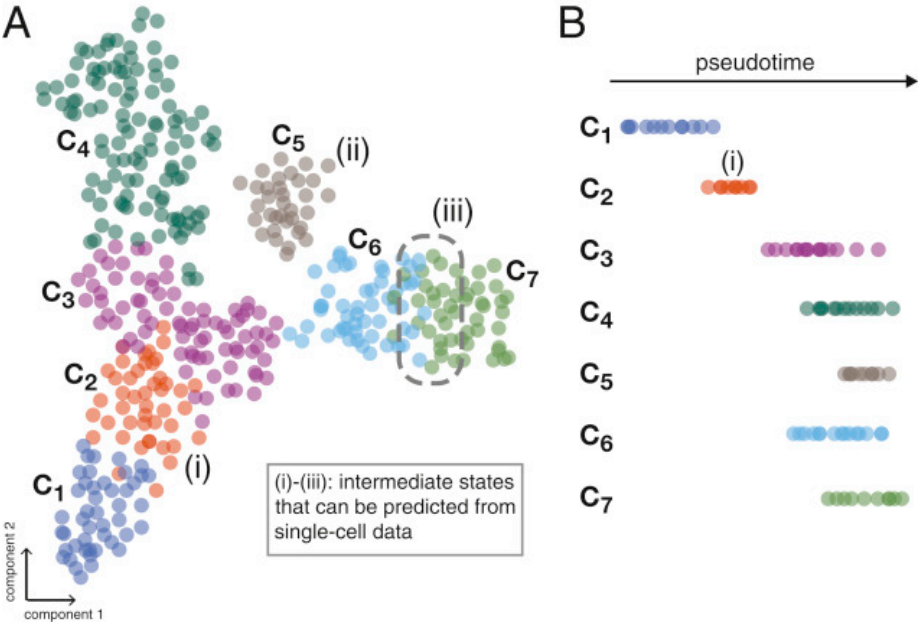

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Figure 2. **Methods to predict the existence of intermediate cell states (ICSs) from single-cell data.** (A) Single cell data projection (e.g. via t-distributed stochastic neighbor embedding (t-SNE)), with cells labeled by subpopulation (C1 to C7). (B) Cells ordered in pseudotime (an unobserved dimension that measures the progress of cell state transitions) by subpopulation. Three classes of ICS are

postulated from these data (others are by all means possible): class (i) – distinct in pseudotime (C2), may indicate transitioning state; class (ii) – distinct on a low-dimensional projection (C5); class (iii) – mixture of subpopulations (C6 & C7).

It can be particularly challenging to identify an ICS with transient properties, especially since most single-cell data give only a snapshot of time; cells can be analyzed in pseudotime to give hints regarding transience [65] (populations occupying very little of pseudotime may be considered transient). Although preserving distances among clusters of cells in the projections can be useful for subsequent clustering analysis [98], possible ICSs might be lost by using these methods because of the potential bias towards separation of major clusters. If the number of cells in the intermediate state is significantly smaller than the terminal states [71] (a *rare* cell subpopulation), classical clustering or dimension reduction methods are insufficient, and new computational tools are needed to reveal ICSs and their connections to terminal

states 71, 99.

Conclusions

Accelerated by advances in single cell technologies, our ability to characterize cell types is expanding, and new forms of phenotypic diversity are revealed, including the intermediate cell states (ICSs) that lie between traditional categories of cells. ICSs re-ignite debate over how we should define cell types and cell type transitions [100]. Due to a lack of quantitative tools, cells were previously classified based on their morphologies and cell surface marker expression, which can lead to ambiguity and inaccuracy. Single-cell transcriptomics lead to definition of cell types using dimensionality reduction and clustering techniques, but it remains challenging to standardize these methods across multiple biological systems. The existence of many ICSs becomes suggestive of a 'continuum' of cellular phenotypes 14, 52. Although this could be a useful model for understanding certain systems, the implementation of this idea for defining cell types requires more

generalized method development.

Given the importance of ICSs in induced cellular reprogramming and differentiation 101, 102, 103, and their potential to regulate phenotypic switches, we are poised to undergo a transformation in our ability to control cell differentiation *104, 105. Success in these endeavors relies on our ability to provide suitable theoretical models of cell dynamics, and may lead to a renewal of the definitions we give for the cell states that define us.

Acknowledgements

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An expanded universe of cancer targets

2021, Cell

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> …However, these advances are currently limited by the reliance on measuring gene expression (Grosse-Wilde et al., 2015; Tsoi et al., 2018). It is also important to provide a framework to interpret the results from studies of transitions within a complex “landscape” of states (Janes, 2016; MacLean et al., 2018; Neftel et al., 2019). Both

MacLean et al., 2018; Neftel et al., 2019). Both tumor progression (e.g., to metastasis) and sensitivity to therapeutic agents largely depend on the presence of specific stable and meta-stable cell states—both tumor- and microenvironment-related—rather than on tumor histology, genetics, and natural history of the tumor evolution (Kim et al., 2017)....

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4 Equal contribution.