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Review

Genomic and molecular control of cell type and cell type conversions

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ABSTRACT

Organisms are made of a limited number of cell types that combine to form higher order tissues and organs. Cell types have traditionally been defined by their morphologies or biological activity, yet the underlying molecular controls of cell type remain unclear. The onset of single cell technologies, and more recently genomics (particularly single cell genomics), has substantially increased the understanding of the concept of cell type, but has also increased the complexity of this understanding. These new technologies have added a new genome wide molecular dimension to the description of cell type, with genome-wide expression and epigenetic data acting as a cell type 'fingerprint' to describe the cell state. Using these genomic fingerprints cell types are being increasingly defined based on specific genomic and molecular criteria, without necessarily a distinct biological function. In this review, we will discuss the molecular definitions of cell types and cell type control, and particularly how endogenous and exogenous transcription factors can control cell types and cell type conversions.

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1. Defining cell type

The cells of an organism are made up of a limited number of 'cell types' that are reused in different tissues and combine to form organs and systems. For example macrophages, phagocytic immune cells, are found throughout the body,[1] as are connective fibroblast cells.[2] However, defining a cell type, especially now that single cell technologies are revealing ever more heterogeneity between cells,[3] is challenging, and it remains unclear how many cell types there are, or exactly how fine the differences are that demarcate two cell types. There have been several estimates for the total number of cell types in an organism, with numbers ranging from between hundreds to thousands of distinct human cell or subcell types. Classical taxonomic approaches estimated the number of cell types in a selection of chordata as between 99 and 122,[4] and around 200 cell types in humans.[5] Systematic attempts to count cell types, using a variety of techniques, particularly newer gene expression data, generally come to a much higher number of cell types. CELLPEDIA is a human annotated database of cell type, based mainly on taxonomy, gene expression data and text mining of publications, it suggests 2260 taxonomic categories for cell types.[6] CELLPEDIA also uses tissue location to define cell type, which may inflate the total. However, the same 'cell types', isolated from different tissue locations, can show radically different gene expression patterns,[1,2] hence tissue location can also be an important determinant of cell type. CellFinder takes a different approach, using a mixture of database amalgamation, text mining, and human annotation, it comes to a total of 1058 human cell types,[7] and readily concedes there are many more cell types to discover. Cell Ontology (CL) describes 2200 'classes' of cell or sub-cell type, and, like the related CellFinder and LifeMap databases uses cell type definitions to map the cell types into a hierarchical model of development.[8,9] These newer studies put the total number of cell types considerably higher than previous estimates, and the true number of cell types seems to be increasing as researchers develop new tools to more accurately map gene expression and the epigenetic status of cells.

2. Identification of different cell types in the immune system

An illustrative example of how improvements in technology can drive the discovery of cell types is the proliferation of new immune cell types along the T cell lineage (Fig. 1). Initially defined by morphology alone, T cells were indistinguishable from B cells, and were labelled simply as 'lymphocytes', i.e. cells that occupy lymphoid tissue, but they had no known function.[10] Later, they

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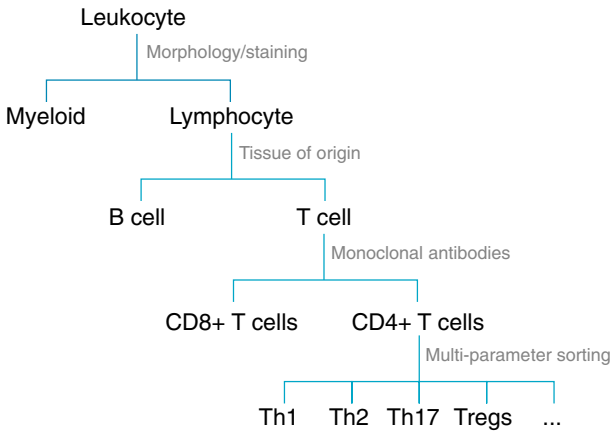

Fig. 1. Gradual refinement of the definition of CD4+ T helper cell types. Schematic of the refinement of the CD4+ T helper cells, from the original cell type 'leukocyte', through to a plethora of distinct Th (T helper) cell types. The technology/technique used to separate the cell types is indicated in grey at the branch point.

were discriminated based on their tissue of origin; bursa of Fabricius-derived lymphocytes (bone marrow-derived in mammals) became B cells, and thymus-derived lymphocytes became T cells.[11,12] However, B and T cells only became recognized as distinct cell types in the 1960s as B cells were definitively identified as the source of the humoral (i.e. antibody) immune response,[11] whilst T cells were initially recognized as 'B cell helpers' a few years later.[13] The widespread adoption of monoclonal antibody technology led to a burst of activity in defining further T cell types. The cluster of differentiation (CD) antibodies,[14] are a set of defined monoclonal antibodies against a variety of cell surface targets. Two CD antibodies can separate T cells into two distinct cell types: CD4+ T helper cells and CD8+ T cytotoxic cells. T helper cells play a supporting role in immune responses, whilst T cytotoxic cells perform cytotoxic killing of virus-infected cells, importantly, their cell morphology is basically identical and they can only be discriminated by their biological activity and cell surface markers. Further application of monoclonal antibodies and careful flow cytometry experiments divided T helper cells into a wide range of other T helper cell types.[15] For example, naïve T helper cells, that have not encountered their antigen are defined by the absence of CD25,[16] whilst experienced (those that have encountered their antigen) T helper (Th) cells differentiate into four major types, namely, Th1, Th2, Th17, and Tregs (regulatory T cells), along with many more less well characterized T helper cell types.[15,17] Importantly, these cell types are not just finer definitions of subpopulations, but each T helper cell type has a distinct biological function. The four best characterized T helper cell types are Th1, Th2, Th17 and Treg cells, which are important in responding to intracellular pathogens, helminth infection, extracellular pathogens, and maintaining self-tolerance, respectively.[18] However, many more T helper cell types have been discovered (e.g. Th9, Th3, TR1, Th22, Tfh, Thab, nTreg, etc.),[15,19] these new T helper cell types have less clear biological roles, but take part in a range of specific activities, including airway inflammation, allergic reactions, B cell responses and immune-related diseases, amongst other roles.[20]

T and B cells were originally defined based on the organ they were first purified from, and the tissue of origin can have a strong influence on cell type. For example, gene expression microarrays of macrophages purified from different tissues showed greater overall variation in gene expression patterns, when compared to other immune cells,[1,21] or compared to just other lymphoid cells.[22] Dendritic cells (DCs), antigen-presenting cells of the immune system, highlight the opposite problem of separating cell types. DCs and macrophages are challenging to experimentally separate accurately,[23] as they share many of the same cell surface markers. Consequently, there is argument about the difference between macrophages and DCs, and a model has been put forward that suggests DCs and macrophages are a 'spectrum' cell type, with phagocytic cells (macrophages) on one end and antigen-presenting cells (DCs) on the other, with several cell types sitting in the middle of the spectrum, each possessing more or less macrophage or DC character.[24,25] Molecular characterization suggests that, from the perspective of gene expression at least, macrophages and DCs can be distinguished based on a unique gene expression signature,[21,26] and macrophages and DCs respond differently to inflammatory stimuli.[23] Yet, arguments over the differences between these cell types remains.[24,27–29]

3. Heterogeneity in embryonic stem cells; defining cell type by biological function

One of the better studied cell types are mouse embryonic stem cells (mESCs), which are derived from early embryos, and maintain the ability to regenerate a full mouse.[30] Although mESCs have many similarities with the inner cell mass (ICM) of the early blastocyst, particularly in the activity of key transcription factors such as OCT4, SOX2, KLF4 and NANOG,[31] there remains debate about their exact origin and cell type,[32] as when the ICM converts to mESCs the cells undergo many gene expression changes.[26,33] mESCs as a cell culture were thought to be relatively homogenous, yet careful study of mESCs revealed small numbers of cells in a typical cell culture with altered gene expression profiles.[34,35] In mESCs, the expression level of the essential pluripotency gene *Nanog*[36,37] naturally fluctuates, and about 5–20% of mESCs express very low levels.[37–39] In culture, mESCs cycle *Nanog* on and off, which helps prime mESCs to differentiate,[39] and so these cells have a distinct phenotype and arguably cell type. *Nanog* is by no means the only example of heterogeneity in mESCs. STELLA, a marker of primordial germ cells, is expressed in 20–30% of mESCs, and those cells with STELLA more closely resemble the ICM, whilst those without STELLA express developmentally later epiblast-specific genes.[40] Indeed, there are multiple cell types contained within a typical mESC culture, including small numbers of cells with radically different biological function. Normally, mESCs very rarely contribute to extraembryonic tissues, such as the trophectoderm (placenta) or primitive endoderm.[30,41] However, mESC cultures contain about 15% of cells that are *Hhex*+ (a homeobox protein that specifically marks endoderm), and these cells can contribute to extraembryonic tissues in mouse chimeras.[41] Although the *Hhex*+ and *Hhex*-mESC's gene expression signature is nearly identical,[26] they have different biological potential, and so can be considered a distinct cell type. One caveat is that these *Hhex*+ cells still contribute to the epiblast and embryo proper, so it is not a pure population of cells. A rarer subset of cells within mESC cultures express the endogenous retrovirus MERVL. MERVL is specifically expressed at the 2 cell stage of embryonic development,[42,43] and using a MERVL-Tomato reporter, the ~2% of mESCs that express MERVL can contribute to extraembryonic tissues,[43] although again, the MERVL+ cells can also contribute to the embryo proper, and the cells can interconvert between MERVL+ and MERVL- cells,[43] suggesting instability in their cell type. It was initially thought that these MERVL expressing cells closely resemble the 2 cell (2C) stage of the embryo, where MERVLs are also specifically expressed,[43] however, recent single cell RNA-seq data suggests these 2C-like cells may more closely resemble the blastocyst, so their ultimate identity remains unclear.[35] Ultimately, the relationship between all of these heterogeneous cell types or sub-cell types within mESC cultures remains unclear. For example, despite their capability of both 2C-like and

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