Journal of Cell Identity

Fostering a concept:

Why cell identity matters

Mihail Eugen Hinescu

‹‹Keep in mind that the human body is made up of trillions of cells, also keep in mind that just one living cell contains over thirty thousand proteins of one hundred different configurations… making chemical compounds at a rate of a million reactions "per second". We can't build a city that can do that.››

Dedivonai, 2012.

‹‹Identity can be a complicated matter.››

Descombes, 2016

Abstract

The aim of this editorial is to examine if and why a new journal focusing on issues concerning identity in general, cell identity, or cell-group identity could offer a new perspective or better vision in cell science. Recent advancements in technology (single-cell -omics) and the high amount of data and perspectives provided by the former experience in other domains of science (mainly social sciences) could offer at least some answers and, more importantly, allow new questions in biology and life sciences. Issues such as diversity, identity management in cells, and conservation versus change of identity, reprogramming, identity control, or identity recognition, may be interpreted or analyzed in a more complex manner if regarded form the perspective of the concept of identity. Deciphering what mechanisms stabilize or regulate cell identity could be crucial in understanding cell behavior. Learning how different pathogens or transformed cells hijack mechanisms involved in maintaining cell identity may offer, from a practical point of view, models or instruments to imagine means of control and maintain or manipulate cell identity during development, physiology, or disease. This opening article in the Journal of Cell Identity briefly mentions some of the emerging ideas concerning cell identity and is intended as a starting point for debate and analysis of more aspects concerning cell identity in health and disease.

Keywords

Cell identity; cell type; cellular state; cell identification; cell atlas; reprogramming

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A pattern of complexity: cell diversity

Morphological sciences (histology and histopathology) are disciplines by tradition based on microscopic features of cell types and tissues. Currently, diagnosis is certified on histo(patho)logical evidence obtained during or at the end of a clinical investigation, if possible. In certain severe diseases (e.g., cancer), treatment cannot be started before histopathology is available. However, most current forms of microscopic imaging, including immunohistochemistry, immunofluorescence, and confocal microscopy, provide information only on cell phenotype and positioning at a particular moment. Live cell imaging is the only form allowing the collection of information relevant to establishing lineage, state, or plasticity. However, mechanisms underlying the stability of cell identity are not discoverable, even with this approach.

Inspired by the semantic technology, Fig. 1 outlines the basic data for better processing of concepts contributing to defining the notions of cell type and cell identity.

The balance between the complexity and relevance of recent tools to address specific functions and features of different cell types is a contributing concept in oncology drug development. For example, modification of nuclear pore complexes could emerge as a regulator of cell identity (Gomar-Alba et al., 2020).

How diversity arises is best illustrated by recent progress in embryology. "*The derivatives of these lineages are regionalized in domains defined by their position along the embryonic body axes... The population of embryonic cells expands rapidly from ~15 ICM cells in the blastocyst, to about 400,000 cells in the early organogenesis stage embryo, and around 13 million cells in the organogenesis stage embryo*" (Tam and Ho, 2020).

Well-known cell types contain a number of diverse cell subtypes, some of which are able to differentiate into a number of cell lineages with great potential for regenerative medicine. This diversity in cellular identity may underlie regional differences in adipose tissue (Trevor et al., 2020), in white and grey brain areas (Werkman et al., 2020), or in cell residents in "hematopoietic niches" (Gomes et al., 2020).

More and more new techniques and strategies have been developed in order to better identify/tag cell types and subtypes. They have been grouped into three main strategies based on live imaging, prospective and retrospective cell lineage tracing, and single-cell RNA sequencing (for review see Cheung and Rizzoti, 2020). Anticipating (and manipulating) cell behavior patterns (i.e., cell habits) and examining the balance between lineage determinants and microenvironment seems to be the ultimate goal of these developments.

With the establishment of the concept of cell identity, phenotype analysis has become more complicated than ever. A better understanding of cells' "self-stabilizing core regulators of identity" could guide provocative developments in cell science in the near future.

Relationship between cell identity, cell state, and behavior

Starting from an approach based only on the simple extrapolation of data in a reductionist context, the practice of changing plans is increasingly prominent in the medical literature. Cell behavior is seen as a result of the *state of identity* and could mean the plan stays the same but identity matters more for interpretation. Better knowledge of identity will allow better understanding of behavior.

Asking difficult or revealing questions does not exclusively concern the technical side of research. Sometimes, when starting with a new vantage point, a new paradigm could develop. "*Do we need new observables in the world of life or not? This point is crucial, and the different paradigms of biology are nothing less than different ways to answer it*" (Barbieri Paradigms of biology).

Identity could be one of the new observables at the cellular scale, promising unexpected developments in the way we think of the cell world. Cell behavior may help in

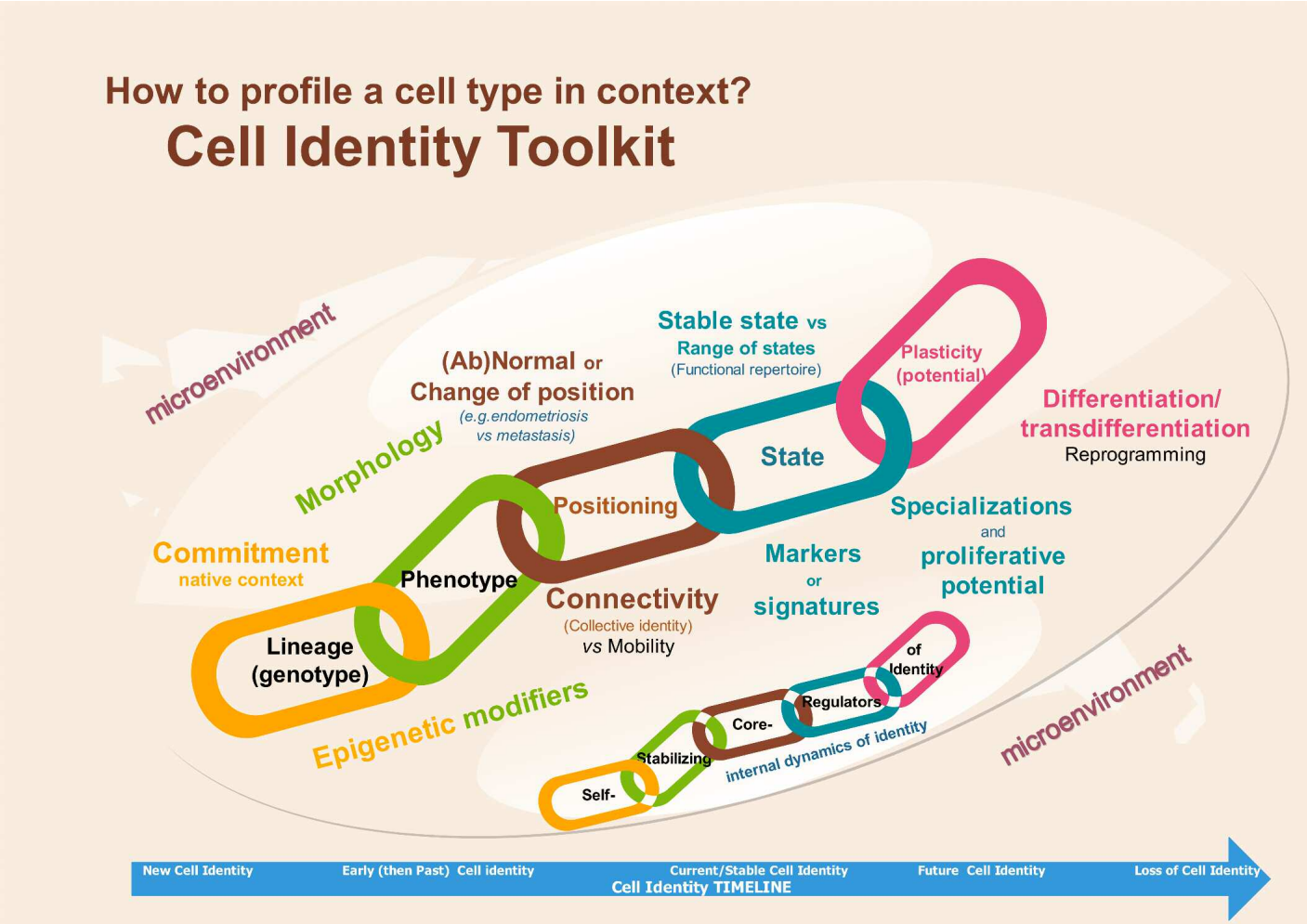

Figure 1.
Concepts and associations currently in use to better define and understand cell identity.
Adapted from Goessling, 2019; Mincarelli et al., 2018; Mukamel and Ngai, 2019; Zi, 2018; Morris, 2019.

drawing a cell-type identity, but it also possible that identities reflect the behaviors in which the individuals engage (Burke, 2003).

By analogy with the concept of meta-identity used in social sciences (Shepherd and Patzelt, 2018), one may infer that cells sharing functions, communicating locally, or being activated together in a tissue/organ are exercising their highest level of identity, a meta-identity. This could explain why, in a different environment, their phenotype changes, reverting to a lower/basic level of identity. Furthermore, a "reversible switching between varying states of competency in the absence of any genetic modification" has been described in bacterial populations (Ikryannikova et al., 2019).

In experimental setups, cells sometimes behave in unexpected ways. When an explanation is available, it is often impossible to verify. Other times, the explanation is that expectations were tuned to an experimentally *misidentified* cell type or ignored the meta-identity. Despite their abstract nature, such observations may help interpret unpredicted experimental results.

Medicine is a *science and art* of manipulating cells and "cell societies"

Despite the fact that cells evolve complex mechanisms to manipulate different things, including time, they can be easily manipulated or hijacked (Philips et al., 2013). Starting from an aphorism of Sir William Osler describing medicine as "a science of uncertainty and an art of probability", one may say that, in the 21st century, medicine became a science of *precision* and an art of manipulating cells and "cell societies".

One note published by Kobe University is informative about one of the most sophisticated instruments recently created to control cell behavior, a microscope allowing holographic manipulation of cell networks with light in order to assist in reconstruction of a

nerve. Such an example illustrates the range of the instruments designed for cell manipulation. It has become almost a truism that pharmacology is a strand of manipulation of cellular behavior during disease (Baillie et al., 2016; Moga et al, 2016) based on the apparent honesty with which individuals advertise their quality. However, this observation is particularly puzzling when the interests of signalers and receivers are in conflict (Biernaskie et al., 2014) and is not applicable at smaller scales, such as tissue (collective individuals) or single cells.

Manipulation includes a variety of techniques, including the simple use of false signaling (either chemical, electrical, or complex messages), the use of "non-manipulated cells" originating from adipose tissue (Guillaume et al., 2020), manipulation of cell networks *in vivo* via integration of bioelectricity with mechano-biology (Leronni et al., 2020), altering microgroove-based topographies that can influence the motility of normal and cancerous cells differently (Yaginuma et al., 2020), microfluidics manipulation of the extracellular microenvironment (Chen et al., 2020), and manipulating the survival of bacterial communities (Ikryannikova et al., 2019).

Telling lies to cells has become almost standard procedure in therapy. The procedure is continuously evolving, using drugs to light, but is still engrossing. Cells do not care about the good or bad, and when normal, do not have apparent individual interests. This would result in dishonest behavior in a cell society (Reynolds, 2014).

Forced to listen, cells are just the target of manipulation, but telling secretes to unidentified could be dangerous.

Misidentification is probably the most currently overlooked implicit bias in cell science

Whenever a patient (*i.e.*, a person diagnosed with a clinical form of disease) does not respond to treatment, one may inquire about the identification of the disease and implicitly, about the alteration(s) at the cellular level. Were all cell types present at the lesion accurately identified? Was the examined tissue fragment representative enough? Were enough fragments examined (e.g., during a biopsy)? Was the histopathological analysis appropriate and all current criteria fulfilled? Furthermore, are all necessary criteria adequately formulated in the guidelines? How many criteria are sufficient for accurate identification? Why are guidelines so frequently revised? Was treatment personalized? To move the field of precision medicine forward, we need to be aware of identity and identification limits.

These questions, and many others, that a reader could easily ask underline the crucial importance of appropriate identification. How do you achieve accurate identification when cellular identity is not (yet) sufficiently defined? When a paper mentions that a study was conducted using a specific cell type, conclusions are drawn, but the criteria for identification are frequently not mentioned. For example, the fibroblast is a widely distributed cell type examined in a lot of studies and involved in different diseases. A recent study stated, "Emerging data point to functional heterogeneity of fibroblasts. However, the lack of sub-type specific markers hinders our understanding of the different roles of fibroblasts in ECM biology, wound healing, diseases, and aging" (Worthen et al., 2020).

How then do we compare the behavior of a cell type during different circumstances in the absence of accurate identification?

Organoids and engineered tissue/organs represent an expanding area. Precise information about cell identity is a pre-requisite for studying or constructing either tissue for substitution or replacement disease models. On the other hand, in an attempt to understand the development of cell identity, organoids brought to light an emphasis on "the interplay between metabolic identities" (Rodríguez-Colman, 2017), or "shifting cell identity" (Jadhav and Shivdasani, 2019).

Identity in the "multi-omics" era

"Identity can be a complicated matter" (Descombes). In life sciences, accurate identification appears to be more important than knowledge of the (true or full) identity. Simple observation is consistently missing in papers we are currently reading, as identification has to rely on appropriate knowledge of identity. Too much approximate premises may lead to false identifications. One may ask why no guideline exists for accurate cell identification. The Human Cell Atlas initiative, launched in 2016, illustrates the need to "describe and define the cellular basis of health and disease" (Human Cell Atlas, 2020; Rozenblatt-Rosen et al., 2017; Pullen, 2018).

An array of projects are aiming to build cell atlases, including the cell mouse atlas (Tabula Muris Consortium, 2018), embryo development atlas (Castro-González et al., 2012; Hescheler et al., 2006), brain cell atlas (Ecker et al., 2017), brain connectivity cell atlas (Kuan et al., 2015; Eastwood et al., 2019), brain transcriptome atlas (Mahfouz et al., 2017), an atlas of transcriptomic cell biology (Tabula Muris Consortium, 2018; Rozenblatt-Rosen et al., 2020), and Cancer Genome Atlas (TCGA) by the NCI program (Hutter and Zenklusen, 2018). All of these programs or initiatives derived from the "multi-OMICS era" (de Anda-Jáuregui and Hernández-Lemus, 2020) are currently providing a large number of individual traits on the cellular scale in order to better identify and predict cell behavior(s) or responses to treatment during disease, helping us understand heterogeneity and clarify cell diversity.

Comparative approaches are largely based on the differences in individual traits (Tang et al., 2020), but there is an acute need for a hierarchy when it comes to elaborate criteria or guides for cell identification. Most accurate could mean most difficult (or even impossible) to use on large scale projects.

Thus, accurately defined and standardized means of identification provide a basis for manipulating the epigenotype, genotype, phenotype or signaling.

Identity Games: From fake recognition to identity shift, theft or reprogramming

"Organic information and organic meaning, in short, belong to the same class of natural entities because they have the same defining characteristics, but what exactly are they? What is it that they have in common and what is it that differentiates them from the other entities of Nature?" (Barbieri, 2016).

Starting from these observations, let's apply/adapt them to the concept of cell identity. What is the code behind the development, maintenance, and decay of the identity of a cell or a group of cells? How is it linked to the conflicting chemical paradigm and information paradigm in biology? Will it be possible to define an identity code for cells, or it will remain just a metaphor?

Is identity an important concept playing a role in cell physiology? What are the physiological mechanisms based on identity recognition? How can identity be mimicked, hijacked, or recovered at the cellular level? When collective cell identity is altered, is it a reversible event? What are the consequences of malfunctioning during cell identity-based mechanisms? What is the role of such mechanisms during development or during disease? What controls appropriate identity maintenance or cell recognition/identification? Is there, by analogy with programmed cell death, a programmed cell identity cycle? How is this program controlled? What are the consequences of reprogramming cell identity?

Such questions are seldom asked, or so we already have some answers in the scientific literature? Are today's scientists prepared to answer leading questions on cell identity or eager to seek answers?

Our pre-planned response is to offer a place for such scientific debates in this new journal, *Journal of Cell Identity*.

Why a journal about cell identity?

In his book, "Lateral Thinking", Edward Bono noted that, "*The attention area is limited and includes much less information than is available. If something is left out of consideration then there is nothing which will make it come back into consideration at a later point. What is there does not usually indicate what is missing. Attention usually settles over the most obvious areas*." Today, identity and (accurate) identification represent a good (still unusual) point of view (frequently overlooked) in examining cell societies. Despite an obvious increase in the last few years in the number of articles dealing with cell identity, a journal focused on this issue has been missing.

An approach from a new perspective has been missing in life sciences despite (or just because) many (social) sciences use this approach: "Understanding the mechanisms through which social identities motivate behavior and understanding the relative durability of specific identities as such are two of the major goals driving scholarship" (Kalin and Sambaris, 2018).

The dividing line in *Clarivate Analytics* databases between *Science Citation Index Expanded* (1975-present) and *Social Sciences Citation Index* (1975-present) underlines the contention of specific approaches in the two separate categories of science publication. For a long time, identity was much more useful in social sciences, but now it appears to be an appealing (new) type of approach in (the more) exact sciences.

In addition, only recent advancements in cell science have made it possible to examine huge amounts of (single) cells in order to classify/identify specific types (Mincarelli et al., 2018; Biddy et al., 2018; Islam et al., 2020; McKinley et al., 2020). There are many existing journals that publish appreciable amounts of results and points of view in cellular science that mention identity or identification, but none are centered on examining aspects concerning structure, function, or the potential of manipulation from this very specific and complex perspective of cell identity.

"*As we head into the future, one Yogi-ism to avoid is: You've got to be very careful if you don't know where you are going, because you might not get there*" (Cox, 2010).

Finally, we hope that you (the readers and future authors) will write to us, send us manuscripts, and help make the *Journal of Cell Identity* a rigorous, easy identifiable, long-living publication in a specific niche, contributing to the creation and sharing of knowledge about the identity and identification of cells with an impact on life sciences and health care.

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