Commentary

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Nomenclature for cellular plasticity: are the terms as plastic as the cells themselves?

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It is now recognized that cell identity is more fluid, and tissues more plastic, than previously thought. The plasticity of cells is relevant to diverse fields, most notably developmental and stem cell biology, regenerative medicine, and cancer biology. To date, a comprehensive and uniform nomenclature to define distinct cell states and their injury-induced interconversions has been elusive. The first Keystone Symposium devoted exclusively to cellular plasticity in regeneration and tumorigenesis was held on January 2019 in Keystone, Colorado, and featured a workshop on terminology in the cell plasticity field. Definitions for terms such as plasticity, de- and transdifferentiation, reversion, and paligenosis were discussed. Here, we summarize the content and tenor of the symposium and nomenclature-focused workshop with regard to terms in the field. We outline the challenges with current definitions and recommend best practices and approaches to developing an accurate and acceptable nomenclature in the future.

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Changes in cellular identity are an intrinsic feature of development in multicellular organisms: as cells differentiate from progenitors to progeny, they acquire increasingly specialized features. While cells are thought to maintain their differentiated features in adult tissues under stable (homeostatic) conditions, cellular identity becomes plastic when tissue homeostasis is perturbed (e.g. during injury/inflammation). The Keystone Symposium "Cellular Plasticity: Reprogramming, Regeneration and Metaplasia (J3)", held on January in Keystone, CO, was the first conference fully devoted to understanding how cells change their identity ("reprogram") in physiologically relevant settings. During the meeting, and specifically during a workshop devoted to the issue of nomenclature, it emerged that a common language describing features of cellular plasticity is needed for researchers to share results across tissues, model organisms, and experimental platforms. Here, the authors, co-organizers of the Keystone meeting, synthesize discussion that took place during the meeting to set the stage for a broader, ongoing exchange on vocabulary in the emerging field of cellular plasticity.

The most common terms to describe cell plasticity have been in use for decades. For example, Rudolph Virchow delivered one of the first lectures on cell plasticity in 1886 (Virchow, 1886), coining the term Metaplasia to describe the pathological lesion in which cells acquire an identity that is unusual for a given tissue while still retaining normal cellular features (i.e., no dysplasia or neoplasia). He called such conversions "plastische Prozesse" ("plastic processes"), likely one of the first instances of the term Plasticity to describe cell type switches in an adult tissue. The term describing a manifestation of Cell Plasticity wherein a cell returns to either a more progenitor- or embryonic-like state, Dedifferentiation, was described already by 1900 and mentioned as a specific term in German ("Entdifferenzierung") in 1908 (Adami, 1900; Adami & Nicholls, 1908). From the developmental biologist's perspective, a cell is thought to dedifferentiate when it ceases to perform certain specialized functions and readopts the identity of a stage it had previously passed through during its differentiation (Fig 1), although as we will discuss below, this definition may be overly restrictive. Transdifferentiation is a term that emerged in the 1960s and 1970s (Weissenfels & Hündgen, 1968; Coggin & Anderson, 1974; Okada, 1975) and is commonly defined as the process wherein a cell phenotype switches from one mature or differentiated state to another without dedifferentiation (Fig 1).

The Keystone meeting brought together diverse investigators, which spotlighted how the application of these terms can vary widely among fields of study despite a decades-old etymological history. For example, terms have been introduced and employed by pathologists (such as Adami and Virchow) and geneticists (Thomas Hunt Morgan and Conrad Waddington), working at different times and without a consistent framework (Virchow, 1886; Adami, 1900;

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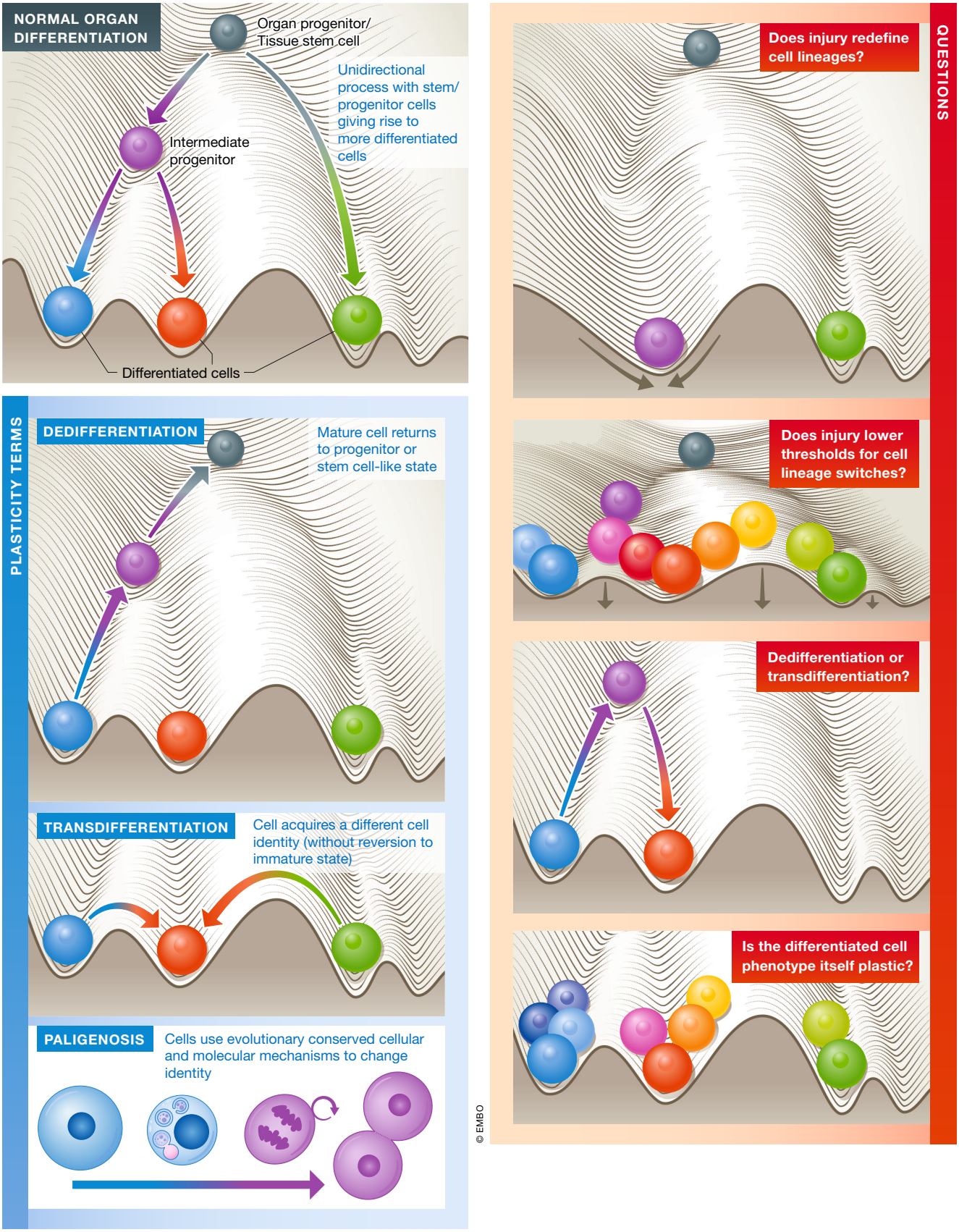

Figure 1.

Figure 1. Cell plasticity within an adult tissue: common terms and problematic aspects illustrated.

An adapted tissue differentiation "landscape" in an adult tissue with an active stem cell is depicted as envisioned by Waddington with several differentiated cells in grooves at the "bottom" of the landscape implying terminal differentiation. The stem cell has potential to roll down several grooves ("differentiate") into each of the adult cells. A progenitor cell with more limited differentiation options is also depicted. "PLASTICITY TERMS"—commonly used terms in cell plasticity are illustrated as events on the landscape with canonical definitions in blue. Note: Paligenosis describes the cell biological process of converting a mature cell into a regenerative cell, regardless of tissue or "position" on the landscape, so it is not depicted on the landscape. "QUESTIONS"—illustrates scenarios that may not be covered by current terms or that may highlight how current terms can overlap. Inflammation or injury can either change the grooves (i.e., redefine what stable cell lineages are in the tissue or simply lower the threshold for interconversion among different mature or progenitor cell types). Single-cell analyses like RNA-Seq suggest that mature cells may be relatively fluid even in steady state such that differentiated cells are not as fixed in a single groove as has been implied by traditional fixed tissues and histological approaches. Transdifferentiation may occur via a dedifferentiation process.

Adami & Nicholls, 1908; Morgan, 1922; Waddington, 1956, 1957). Ambiguities in usage persist today: though each investigator at the meeting seemed confident in their own definition of a certain term, other investigators stood firm with distinctly different definitions. Given the growing recognition that cellular plasticity is important in numerous physiological and pathophysiological contexts, it is imperative that researchers, journal editors, and trainees employ a shared language. Common terms are needed to describe how mature cells change phenotypes in different contexts: e.g., tissue injury (Kopp *et al*, 2016), induced cell reprogramming (Graf & Enver, 2009), as well as cancer cell plasticity (Varga & Greten, 2017; Gupta *et al*, 2019; Yuan *et al*, 2019) see also (Mills & Sansom, 2015; Merrell & Stanger, 2016).

An overarching issue with defining terminology that emerged during the meeting was that understanding plasticity means understanding cell identity. However, cell identity can be defined in multiple ways, thereby creating a paradox. Traditionally, specific cell types have been defined by histology (i.e., based on the location and staining characteristics of cells in tissue) or developmental lineage (i.e., understanding how such cells arise). As discussed below, whether a histopathological or developmental biological approach is taken to define cell identity has an impact on how one distinguishes dedifferentiation from transdifferentiation. More recently, advances in single-cell analysis have further complicated the definition of cell identity, revealing substantial transcriptional heterogeneity among cells within traditionally defined cell types. Hence, cells with seemingly homogeneous morphological features likely exist in different (and possibly constantly shifting) states, giving them a substantial degree of plasticity that traditional methods of defining cell identity failed to recognize. Additionally, epigenomic analyses have shown that transcriptionally similar cells can differ in underlying chromatin state, thereby affecting responses to environmental cues. In short, classical definitions of cellular identity based on histological or developmental considerations reflect a concept of static cell states. In reality, tissue-resident cells experience large-scale fluctuations in gene expression in quotidian fashion, but we miss these fluctuations if we do not observe cell states dynamically in living cells in their tissue context. In injured tissues, cellular identity becomes even harder to define (Fig 1). For example, the "pulleys" and "guy wires" that shape the "grooves" (i.e., cellular identities) in Waddington's metaphorical landscape of cellular differentiation may change when tissues are injured (Fig 1), thereby further obscuring predefined concepts of cellular states in ways we do not yet understand (Rajagopal & Stanger, 2016).

Thus, one take-away from the Keystone meeting is that notions of plasticity are rapidly evolving, making it important for definitions to retain some flexibility as the field accrues a deeper understanding of cell state dynamics in living tissues. In the rest of this editorial, we discuss in more detail the definitions, nuances, and issues with several of the common terms in hopes that this will serve as a reference point for further elaboration as the science evolves. First, we note that there seems to be general agreement within the field about the term "Cellular Plasticity" itself, a term that generically captures changes in cellular identity or phenotype that occur outside normal development and tissue homeostasis. As mentioned above, plasticity is perhaps one of the oldest terms to describe changes in cell state or cell type, employed first by the pathologist Virchow in the 19th century. In many ways, Metaplasia is one manifestation of plasticity (at the tissue level), which is why Virchow used metaplasia and plasticity almost interchangeably. Surprisingly, the geneticist and developmental biologist Waddington, who developed the concept of a unidirectional differentiation landscape with predefined strict cell identity "grooves" (Fig 1), also used metaplasia to describe regenerative plasticity in tissue (Waddington, 1956). However, metaplasia now is a term predominantly used by pathologists to describe cell plasticity within the context of disease.

Dedifferentiation is commonly visualized on the Waddington differentiation landscape as a cell losing its differentiation state as it "rolls uphill" to a prior progenitor or "stem-like" state (Fig 1). The trouble with the term, however, is that there is no consensus regarding the extent to which a cell must exhibit progenitor or embryonic features to determine that it has reverted to an earlier developmental stage. Is re-expression of one or two ancestral markers or transcription factors enough, or must there be a documentable global shift in gene expression? Can dedifferentiation be defined by transcriptional changes alone, or should the term also indicate chromatin rewiring or changes in cellular function? An additional concern is that the term has a different meaning in the context of cancer pathology, where the words "dedifferentiation" and "dedifferentiated" are used to describe malignant tumors that have unusual features that do not correspond to any physiologically normal cell state. In other words, a dedifferentiated or poorly differentiated tumor to a pathologist does not necessarily mean that this tumor exhibits features of embryonic progenitors. In settings where cells lose their differentiated phenotype without acquiring the full complement of properties associated with a pre-existing progenitor state, one agnostic approach might be to use a different term, like "undifferentiation".

Like dedifferentiation, Transdifferentiation as a term is conceptually straightforward. In tissues, however, the application of the term can be complex (Fig 1). For example, how extensive must the evidence be that differentiated cell A has become differentiated cell B? How does one prove that there was no temporary return to a less-

Box

Concept	Caveats
Normal Organ Differentiation	• Most adult tissues (e.g., pancreas, liver) lack dedicated stem cells • Cell plasticity may drive regeneration • In stem cell-devoid organs what do mature cells dedifferentiate into?
Dedifferentiation	• Criteria to define dedifferentiated state (i.e., molecular, functional, or both) • Term also used by pathologists to describe cancer phenotype unrelated to developmental reversion • Part of homeostasis or solely driven by injury?
Reversion	• Unclear how reversion differs from dedifferentiation
Transdifferentiation	• Is it transdifferentiation if a cell dedifferentiates before redifferentiating? • Can transdifferentiation involve mitosis? • Criteria to define complete cell conversion to new fate are unclear (i.e., molecular, functional, or both)
Metaplasia	• Term defined at tissue, not cellular level • Imprecise, referring to any type of plasticity in disease context • Is this a reversible or permanent process?

differentiated, progenitor-like state before a "redifferentiation" to the differentiated alternative fate (Fig 1)? Would the process still be called transdifferentiation if the cell transitioned through a less-differentiated intermediate, which was an issue raised even relatively early in the history of use of this term (Coggin & Anderson, 1974)? If cell division occurs during the transition, does this no longer count as transdifferentiation? As discussed above, single-cell analyses are revealing that an adult tissue cell type may actually comprise a diversity of potential cell identities with features that outstrip historical cell lineage definitions (Fig 1). In other words, it remains unclear how different cell A must be from cell B for a phenotypic switch to be considered "transdifferentiation". Likewise, how many of cell B's features must be adopted (at the single-cell level) by cell A to meet the definition of transdifferentiation?

Other terms describing cell plasticity include "Reversion" which has been used to denote when a mature or quiescent cell returns to a stem cell state (Lane *et al*, 2014). It seems to be used predominantly by scientists studying adult differentiation and injury response in the intestine, though there is precedent for reversion as a general term meaning dedifferentiation as early as Adami (1900). Reversion largely appears to be synonymous to dedifferentiation, though reversion seems to be used more specifically to denote return specifically to the adult tissue stem cell state vs. return to progenitor or embryonic states. Paligenosis has been used by one of us to describe the process, at the cell biological level, used by a mature cell to change identity (Willet *et al*, 2018; Fig 1). Paligenosis was proposed to define the specific, evolutionarily conserved molecular machinery cells use to dedifferentiate or transdifferentiate. Similar to how apoptosis focuses on specific program cells use to die, paligenosis focuses on the program cells use to change cell type (Messal *et al*, 2018).

Although many of the terms used in the cell plasticity field are old, their usage is evolving as we learn more about the cellular state changes that cells can undergo in various disease states. A consensus will emerge with time through ongoing discussions between workers in the field. We summarize our recommendations, based on discussions with attendees at the Keystone Plasticity meeting as follows: (i) The term *cellular plasticity* is a useful umbrella term for the field to describe cell identity changes. (ii) Common terms like *dedifferentiation* and *transdifferentiation* can mean different things to different investigators. As authors, we should define exactly how we are using specific terms at the outset of our articles, rather than assuming that everyone agrees on a definition. As editors and reviewers, we should realize that definitions are in flux and that we should not insist on a specific definition as long as the authors *a priori* define their usage of the term. We look forward to engaging with our colleagues on this issue. We welcome any suggestions via journal Twitter account: https://twitter.com/emboj ournal.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

Adami JG (1900) On growth and overgrowth. In *"Festschrift" in honor of Abraham Jacobi, MD, LLD: To Commemorate the Seventieth Anniversary of His Birth, May Sixth*, Huber F, Sondern FE (eds), pp 422–432. New Rochelle, NY: Knickerbocker Press

Adami JG, Nicholls AG (1908) *The principles of pathology*. Philadelphia, PA and New York, NY: Lea & Febiger

Coggin JH, Anderson NG (1974) Cancer, differentiation and embryonic antigens: some central problems. In *Advances in cancer research*, Klein G, Weinhouse S, Haddow A (eds), pp 105–165. Cambridge, MA: Academic Press

Graf T, Enver T (2009) Forcing cells to change lineages. *Nature* 462: 587–594

Gupta PB, Pastushenko I, Skibinski A, Blanpain C, Kuperwasser C (2019) Phenotypic plasticity: driver of cancer initiation, progression, and therapy resistance. *Cell Stem Cell* 24: 65–78

Kopp JL, Grompe M, Sander M (2016) Stem cells versus plasticity in liver and pancreas regeneration. *Nat Cell Biol* 18: 238–245

Lane SW, Williams DA, Watt FM (2014) Modulating the stem cell niche for tissue regeneration. *Nat Biotechnol* 32: 795–803

Merrell AJ, Stanger BZ (2016) Adult cell plasticity *in vivo*: de-differentiation and transdifferentiation are back in style. *Nat Rev Mol Cell Biol* 17: 413 – 425

Messal HA, Cremona CA, Lan L, Behrens A (2018) Paligenosis: prepare to regenerate! *EMBO J* 37: e99206

Mills JC, Sansom OJ (2015) Reserve stem cells: differentiated cells reprogram to fuel repair, metaplasia, and neoplasia in the adult gastrointestinal tract. *Sci Signal* 8: re8

Morgan TH (1922) *Some possible bearings of genetics on pathology*. Lancaster, PA: Press of the New Era Printing Company

Okada TS (1975) "Transdifferentiation" of cells from chick embryonic eye tissues in cell culture. *Dev Growth Differ* 17: 289 – 290

Rajagopal J, Stanger BZ (2016) Plasticity in the adult: how should the waddington diagram be applied to regenerating tissues? *Dev Cell* 36: 133 – 137

Varga J, Greten FR (2017) Cell plasticity in epithelial homeostasis and tumorigenesis. *Nat Cell Biol* 19: 1133 – 1141

Virchow R (1886) Congrès périodique international des sciences médicales. 8me session, Copenhague, 1884. Compte-rendu. Librairie Gyldendal (F. Hegel & fils), Copenhagen

Waddington CH (1956) *Principles of embryology*. New York, NY: The Macmillan Company

Waddington CH (1957) *The strategy of the genes*. London: Routledge

Weissenfels N, Hündgen M (1968) Changing adenosine triphosphatase activity in nucleic of cultured chicken heart myoblasts during their transdifferentiation. *Histochemie* 16: 119 – 133

Willet SG, Lewis MA, Miao ZF, Liu D, Radyk MD, Cunningham RL, Burclaff J, Sibbel G, Lo HG, Blanc V *et al* (2018) Regenerative proliferation of differentiated cells by mTORC1-dependent paligenosis. *EMBO J* 37: e98311

Yuan S, Norgard RJ, Stanger BZ (2019) Cellular plasticity in cancer. *Cancer Discov* 9: 837 – 851