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species (*Zea mays*, *Fagopyrum esculentum*, *Arabidopsis thaliana*, and *Solanum lycopersicum*). The resulting groups of orthologous genes (orthogroups) were searched for orthogroups containing genes with expression patterns restricted to a single plant organ. The genes belonging to such orthogroups were analyzed in terms of gene and promoter characteristics thus allowing to infer the common regulatory patterns of tissue-specific genes across wide variety of plant species.

1. A. M. Kasianova et al. (2024) Trans2express—de novo transcriptome assembly pipeline optimized for gene expression analysis, *Plant Methods*, **20**:128

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The concept of cell assemblability

L. Yu. Rusin

*Institute for Information Transmission Problems (Kharkevich Institute),
Russian Academy of Sciences, Bolshoy Karetny per., 19 build. 1,
127051 Moscow, Russian Federation, rusin@iitp.ru*

Since the advent of cell theory in middle 19th century, the diversity of cell kinds has naturally been classed into “cell types” based on their outward (morphological) and/or inner (physiological) properties. While any rigorous phenotypic definition of cell type is inherently lacking, the observable, intuitively distinct cell types, such as animal muscle, neuron, epithelial or stem cells, have traditionally been interpreted as representing elementary organismal units that are directly comparable in evolution and development, and that form according to the same basic logic that underlies the organismal tree of life. Nearly two centuries after, the doctrinal view of cell identity is called into question due to the discovery of key molecular signatures at the level of gene expression in single cells that incontrovertibly demonstrate the presence of backbone similarities that permeate the cells regardless of their structure, form, function or developmental origin, both between-species

and within a same organism. The demand to place this major new fact of life within a theoretical framework is answered by the emerging “cell type theory”, which imputes a primary role to gene regulation in defining the biological nature of cell type. It rethinks the cell type as a population of cells separated from other cells in a multicelled organism via regulation-determined, selective access to common genomic information. Cell type identity is thereby defined as a core set of active molecular regulators of gene transcription (transcription factors), whereas evolutionary change in this core drives the birth and divergence of cell types, determines their genealogy and, hence, innate homology. The emerging regulatory paradigm of cell identity has fundamental implications by providing objective criteria to establish and interpret evolutionary links at the cell level, explaining why and how related cell types can diverge beyond recognition, and demonstrating that cell phylogeny is not equivalent to ontogenetic cell lineage. Although transformative to current biology, this concept still operates with cell types as static and discrete states to describe individual cells, both in evolution and development, which is at odds with the heterogeneity of single-cell data observed at various resolutions and sequencing depths of a single sample or time series, and is not explicative of the cell’s remarkable plasticity to blend and swap functions and flow between states in a cell lineage.

The concept of *cell assemblability* explained here is introduced to provide a more realistic theoretical framework, detailing the sources and mechanisms that shape cell identity in two dimensions, genotypic (in evolution) and phenotypic (in development), via assembly of regulatory circuits as individual “building units”. It rethinks the living cells as *avatars*, transient or terminal cell states deployed in a continuum of states by the developmental programme of one and the same omnipotent cell of the germline (Rusin, 2023), encapsulating the baseline definition of cell type (Arendt et al., 2016) in terms of the basic mechanism for the origin and divergence of novel types via regulatory isolation, whereby a cell type is only equivalent to a molecular cell identity acquired with a newly established (quasi)autonomous regulatory circuit. Meanwhile, it explicitly decouples cell identity from the observable living cell, treating the cell as a dynamic entity that can swap and mix identities, essentially distilling the classical, intuitive cell types (such as muscle, neuron or epithelia) into purely conventional, transient entities, with the

recognition that “cell evolution” and “fate commitment” actually refer to the histories of individual regulatory module transformations and firings, respectively, in the context of a common developmental programme. The concept explains how this logic of cell defines the re-use and redundancy of its “building units” in both phylo- and ontogenesis, enabling the mosaic nature of cell identities and lineages, respectively, governs cell reprogramming and fate transitions (highlighting implications for applied biology and medicine; Zhang et al., 2025), and renders mosaic cell evolution fundamentally different from the vertical evolution of species.

The main statements are as follows:

- 1) The cell is formed with assembly in two dimensions: its identities are irreversibly assembled during evolution at the genomic level from regulatory modules of diverse origins to form a scaffold of ontogenesis, where the cell phenotype is assembled reversibly by swapping, mixing and modifying evolutionary identities to form a versatile diversity of virtually unique cells, possibly including bespoke, non-physiological states that never existed in evolution or normal development.
- 2) The cell is relativistic in terms of an identity with respect to its current regulatory state. This identity can be reassembled seamlessly over large evolutionary distances and a dramatic range of morphology and function, whereby individual cells act as biological avatars operated by regulatory networks of one and the same founder cell, the omnipotent cell of the germline, who interactively morphs to change age, guise and function as the networks are rewired.
- 3) The cell’s assemblability defines the hybrid, mosaic and heterochronic nature of cell identities and lineages:
 - (a) many identities share the same portions of the genome for deployment and are therefore horizontally related in a convoluted and inherently network-like phylogeny – the mode that differs principally from vertical divergence, making cell evolution fundamentally different from the evolution of species;
 - (b) newly invented regulatory modules are usually linked to small cellular functions and can be re-used in multiple contexts during both evolution (in identities with distinct ages and origins) and ontogenesis (in those deployed at distinct times or lineages), producing a diversity of cell types spaced in evolution and development but related by parts of the common genome;

(c) the age of cell identity is decoupled from that of its supporting genes, setting its lower bound at the origin of the youngest genes, while leaving the upper bound open;

(d) the order of identity recall in a cell lineage may differ from their evolutionary succession, whereby older identities may succeed the younger ones.

4) Cell fate transitions are governed by cell transcriptional competency unfolded by pioneer transcription factors:

(a) the competencies are conserved and delineate cell differentiation trajectories into robust developmental tunnels; within-tunnel transitions proceed mechanistically and lineage-autonomously to facilitate developmental redundancy and robustness at the primal cellular level, whereas those across tunnels require specific triggers that induce turnpoint conditions stitching the competencies and their tunnels into a fabric of development;

(b) a turnpoint is theoretically a starting mixture of cell identities induced by a joint action of pioneer factors, which needs not occur in a stem cell;

(c) cell fate transitivity and convertibility depend on the amount of genomic regulatory sites shared between the competencies, thus reflecting the amount of evolutionary distance between them and the cell diversity they support, and defining the type of fate transition, from seamless direct conversion to reprogramming via pluripotency;

(d) the ages of the tunnels and their supported developmental domains are approximated by the ages of the pioneer transcription factors that unfold the underlying competencies.

5) A cell recalls ancestral identities as it differentiates within a competency tunnel, thereby broadly following the recapitulation law of classical biology at the cell lineage level, which states that ontogeny recapitulates phylogeny.

6) The genome stores at least as many instructions for the deployment of ancestral cell types as there are intermediate identities realised in a cell lineage, while some become overridden by evolutionarily newer identities and fossilise as silenced cell types; many fossil instructions are expected to remain, forming the “dark diversity” of cell types that can potentially be resurrected by inactivation of the overriding module regulator gene(s).

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1. L.Yu.Rusin (2023) *Journal of Morphology*, **284**: e21569.
2. D.Arendt et al. (2016) *Nature Reviews Genetics*, **17**: 744–757.
3. X.Zhang et al. (2025) *Advanced Science*, accepted (10.1002/advs.202406208)

Effect of placental serotonin stimulation via maternal signaling on hypothalamic developmental plasticity and offspring's behavior

Marat Sabirov¹, Anastasiia Gainullina¹, Victoria Melnikova¹, Evgeniia Chikina¹, Zakhar Starinnov¹, Elena Shagimardanova², Oleg Gusev², Roman Romanov³

¹*Koltzov Institute of Developmental Biology of the Russian Academy of Sciences, Moscow, Russia, m.sabirov@idbras.ru*

²*Life Improvement by Future Technologies (LIFT) Center, Moscow, Russia*

³*Department of Molecular Neurosciences, Center of Brain Research, Medical University of Vienna, Vienna, Austria
Roman.Romanov@meduniwien.ac.at*

Neurodevelopment is shaped by both genetic and environmental factors, with maternal conditions such as stress and infection impacting fetal brain development through epigenetic mechanisms (Hoek et al., 1998; Brown, 2012; Toth, 2015). Serotonin, beyond its role as a neurotransmitter, serves as an epigenetic modulator during early brain formation (Bonnin et al., 2011; Farrelly et al., 2019). Recent studies suggest that maternal serotonin may act as a transgenerational signal influencing offspring brain organization and social behavior.

To test this hypothesis, we induced a transient physiological elevation of maternal serotonin levels through oral 5-HTP administration in pregnant rats during embryonic days 11 to 14. We assessed offspring outcomes through behavioral assays and performed single-cell RNA