Reversing mesenchymal drift in organismal decline: A new mandate for partial reprogramming

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Reversing mesenchymal drift in organismal decline: A new mandate for partial reprogramming

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The loss of defined cellular identity is a fundamental feature of aging and numerous diseases. This fundamental perturbation is accompanied by a spectrum of context-specific signatures at cellular level, such as the senescence-associated secretory phenotype (SASP) and mesenchymal transition. Building on these foundational discoveries, a recent work by–Lu and colleagues at Altos Labs maps a conserved transcriptional program, termed mesenchymal drift (MD), across human aging and multiple chronic diseases through an integrative analysis of unprecedented scale.[1] Their large-scale profiling reveals a strong correlation between the extent of MD and disease severity. Furthermore, they experimentally demonstrate that MD can be reversed via partial reprogramming, offering novel therapeutic insights for mitigating aging and chronic disease progression (Figure 1).

MD IS A CONSERVED TRANSCRIPTIONAL PROGRAM ACROSS AGING AND DIVERSE DISEASES

The classical transcriptomic shift toward a mesenchymal state has been found in tissue fibrosis and degenerative diseases over the past few decades. The loss of original cellular identity, coupled with activation of pro-inflammatory and pro-fibrotic secretory characteristics (SASP) is also well-established in aging.[2] However, systematic evidence across human tissues has been lacking since R. G. Cutler's "Dysdifferentiation Hypothesis" in the 1980s. Bridging this gap, Lu et al. present the first large-scale multi-omics analysis spanning over 40 human tissues and 20 diseases. Their work demonstrates that this shift extends beyond epithelial cells to the vast majority of cell types—including alveolar epithelial cells, hepatocytes, endothelial cells, hepatic stellate cells, renal tubular epithelial cells, and even astrocytes and oligodendrocytes in the brain. They conceptualize this pan-cellular phenomenon as MD, a process in which cells undergo partial or complete transition, leading to erosion of their original identity while acquiring new or enhanced mesenchymal features (e.g., altered ECM production, cytokine secretion). This systemic identify drift may ultimately contribute to organ dysfunction and disease pathogenesis.

MD is an evolved concept and constitutes a paradigm shift that extends beyond classical EMT and cellular senescence. The classical EMT refers specifically to the acute and localized conversion of epithelial cells into a mesenchymal phenotype in wound healing or cancer. In contrast, MD is a chronic, low-grade, pan-tissue "identity drift" driven by aging. On the other hand, cellular senescence focuses on cell cycle arrest and the SASP, but MD emphasizes the intermediate state for loss of original identity genes and the upregulation of mesenchymal signature genes during aging process.

ScRNA-seq analyses of disease specimens, including metabolic dysfunction-associated steatohepatitis (MASH), chronic kidney disease, atherosclerosis, fibrotic scars, age-related macular degeneration, and inflammatory bowel disease, revealed that MD-associated genes are broadly upregulated across cell types. However, the pattern of upregulation also showed notable cell-type specificity. In MASH, for instance, endothelial cells and hepatic stellate cells exhibited a stronger MD signature compared to other hepatic cells (Lu et al., Fig. 1E). These results point to a potential bias of MD in key cell types during disease progression, which further highlights the correlation between MD and disease severity.

A POTENTIAL BIOMARKER FOR AGING AND CLINICAL DISEASE PROGRESSION

To further validate the association of MD with disease progression and aging, Lu et al. first correlated MD gene sets with clinical outcomes. In idiopathic pulmonary fibrosis, they observed a significant negative correlation between MD expression levels and patient survival time (Lu et al., Fig. 2A). Consistently, analysis of a separate public dataset also revealed that inhibiting EMT factor ZEB1 significantly reduced DNA methylation age (Lu et al., Fig. 2B).

Another notable finding concerns the potential trans-organ effects of MD. The authors observed that circulating proteins associated with EMT/MD (e.g., GDF15, CCL11) were significantly upregulated with aging. Moreover, plasma proteins most strongly correlated with mortality were markedly enriched in EMT-related pathways (Lu et al., Fig. 2E). This suggests that MD originating in a local organ (e.g., liver) may drive the

systemic release of circulating factors, propagating maladaptive phenotypes in distant organs. This "aging contagion" may offer an auxiliary explanation for the rejuvenating effects observed in heterochronic parabiosis studies.[3] In these studies, young blood may counteract aging in older organisms by diluting or neutralizing MD-related circulating factors.

From a therapeutic perspective, this discovery provides novel insights into treating age-related diseases. Conventional antifibrotic therapies typically target terminal-stage myofibroblasts or collagen deposition and have shown limited efficacy. In contrast, targeting MD is expected to prevent the early cellular state transition toward fibrosis. This strategy may also extend to non-fibrotic age-related diseases where MD is implicated, such as Alzheimer's disease (microglia MD) or atherosclerosis (EndMT). Together, these analyses indicate that MD levels correlate with clinical severity and mortality, underscoring its value as a prognostic biomarker and therapeutic target.

THE REVERSIBILITY OF MD: PARTIAL REPROGRAMMING STRATEGY

The landmark 2016 study by Ocampo et al. showed that periodic OSKM induction could reverse aging in mice. Since then, partial reprogramming strategies have consistently been shown to reverse aging hallmarks and ameliorate disease phenotypes across diverse models.[4] Building on the identification of MD as a key process, Lu et al. showed that partial reprogramming interventions downregulate MD-associated genes. This effect was most pronounced with Yamanaka factors, underscoring their specific efficacy against mesenchymal programs in aging and disease. (Lu et al., Fig. 3D).

Furthermore, using high-resolution temporal scRNA-seq and a dimerization-deficient OCT4 mutant, the authors provided compelling evidence that MD suppression and reversal of aged transcriptional profiles occur independently of pluripotency induction (Lu et al., Fig. 6I). This "decoupling" represents a refinement of current therapeutic paradigms. It enables the reversal of aberrant MD states while circumventing the risks associated with full pluripotency acquisition. Thus, this work builds on the foundational principles of cellular reprogramming and outlines a path toward safer, more targeted therapeutic strategies. Meanwhile, building on the successful *in vivo* application of

chemical and transient mRNA-mediated reprogramming over the past decade, it is feasible to develop integration-free reprogramming strategies to reverse MD with a greater safety profile.

FUTURE DIRECTIONS AND CHALLENGES

Building upon prior research, the large-scale integrative analysis by Lu et al. constitutes a translationally significant contribution to aging biology. However, key questions need to be answered. First, while the MD phenomenon is identified during aging, its causal relationship with the aging process is still elusive. A central, unresolved question is whether MD is a primary driver of aging or a secondary consequence. Potential triggers such as TGF-β signaling, SNAIL1, TWIST1, ZEB1, or histone modifications may serve as key candidates for driving MD. Second, the differences in MD reversibility across tissues and the underlying causes of these variations remain unclear. Third, MD strongly correlates with clinical outcomes across multiple diseases. Refining its extensive gene signatures into defined biomarkers could significantly enhance future diagnostic and prognostic accuracy. For instance, in Alzheimer's disease, the observed microglial MD may represent an intermediate state, transitioning from a dynamic immune surveillance role to a chronic, pro-inflammatory phenotype. The molecular signatures of this microglial MD could thus enable earlier diagnosis and create opportunities for timely intervention. Leveraging advanced tools such as artificial intelligence could accelerate the identification of optimal biomarker panels, bridging mechanistic insight and clinical translation.[5] Furthermore, it is urgent to develop more precise, spatiotemporally controllable, and safer strategies for reversing MD. Broad overexpression of all or partial OSKM factors still carries oncogenic risks. Strategies utilizing chemical cocktails to induce partial reprogramming and rejuvenation are under active investigation. They may emerge as a pivotal strategy for clinically reversing MD. In summary, deeper mechanistic insights and additional therapeutic targets are essential for developing effective clinical interventions for complex age-related diseases.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

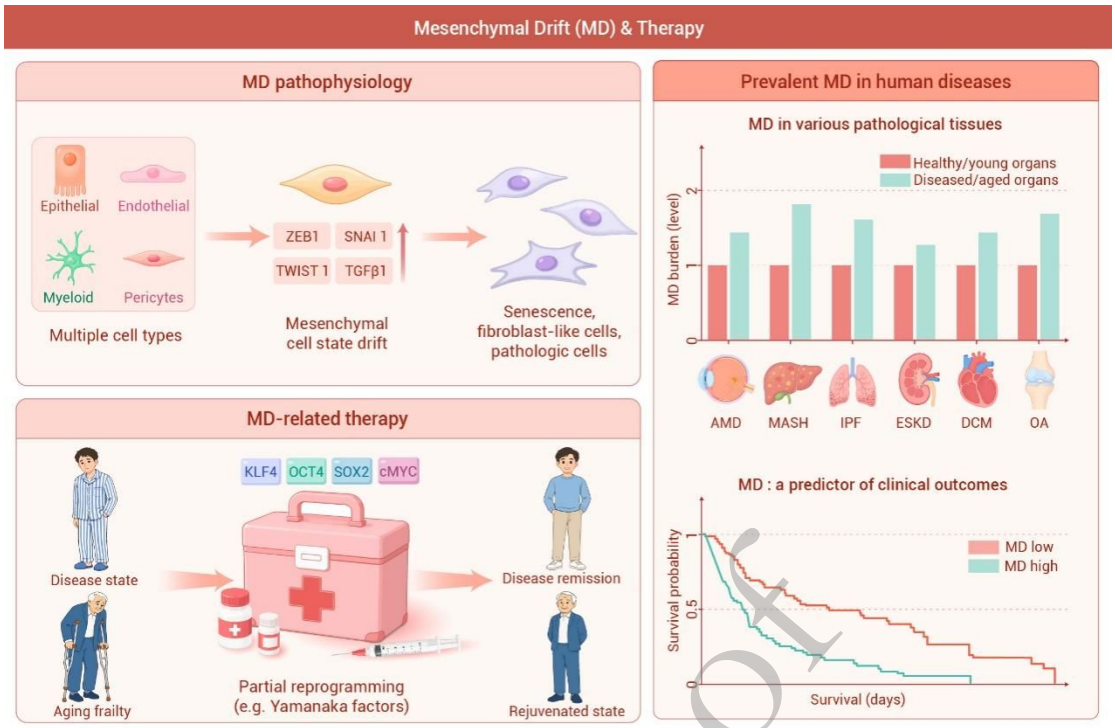
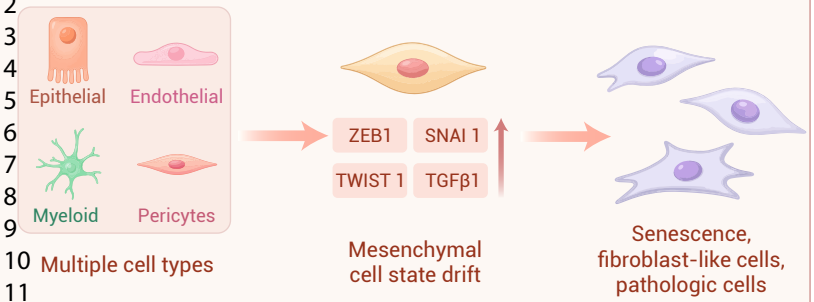
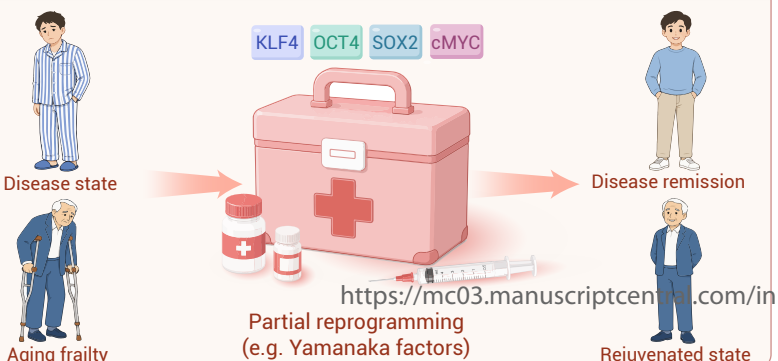


Figure 1. Partial reprogramming reverses MD during organ aging and disease progression. The schematic depicts the reversal from an aged/diseased state to a rejuvenated state by ameliorating MD. Top left inset: various cell types undergo an upregulation of mesenchymal-related genes during senescence, fibrosis, and pathological progression. The top right inset illustrates that MD occurs across various organs and its significant correlation with clinical outcomes. The bottom inset highlights the OSKM-based therapeutic strategies.

MD pathophysiology



MD-related therapy



Prevalent MD in human diseases