REVIEW ARTICLE

A prospective epigenetic paradigm between cellular senescence and epithelial-mesenchymal transition in organismal development and aging

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Q11 **Epigenetic states can govern the plasticity of a genome to be adaptive to environments where many stress stimuli and insults compromise the homeostatic system with age. Although certain elastic power may autonomously reset, reprogram, rejuvenate, or reverse the organismal aging process, enforced genetic manipulations could at least reset and reprogram epigenetic states beyond phenotypic plasticity and elasticity in cells, which can be further manipulated into organisms. The question, however, remains how we can rejuvenate intrinsic resources and infrastructures in an intact/noninvasive manner, particularly in a whole complex aging organism. Given inevitable increase of cancer with age, presumably any failure of resetting, reprogramming, or even rejuvenation could be a prominent causative factor of malignancy. Accompanied by progressive deteriorations of physiological functions in organisms with advancing age, aging-associated cancer risk may essentially arise from unforeseen complications in cellular senescence. At the cellular level, epithelial-mesenchymal plasticity (dynamic and reversible transitions between epithelial and mesenchymal phenotypic states) is enabled by underlying shifts in epigenetic regulation. Thus, the epithelial-mesenchymal transition (EMT) and its reversal (mesenchymal-epithelial transition (MET)) function as a key of cellular transdifferentiation programs. On the one hand, the EMT-MET process was initially appreciated in developmental biology, but is now attracting increasing attention in oncogenesis and senescence, because the process is involved in the malignant progression vs regression of cancer. On the other hand, senescence is often considered the antithesis of early development, but yet between these 2 phenomena, there may be common** Q12 **factors and/or governing mechanisms such as the EMT-MET program, to steer toward rejuvenation of the biological aging system, thereby precisely controlling or avoiding cancer through epigenetic interventions. (Translational Research 2014;■:1–9)**

Q13 **Abbreviations: ■■■ = ■■■**

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INTRODUCTION

A single genotype can give rise to a range of physiologically and/or morphologically adaptive states and phenotypes based on diverse epigenotypes, in response to intrinsic or extrinsic environmental cues and genetic perturbations. We hypothesize that the aging process can be controlled by recalling or sustaining the adaptivity that pre-existed during the early developmental period. Modulating the thresholds and windows of cellular plasticity and its robustness by either genetic or epigenetic approaches, we may be able to conduct certain rejuvenating interventions appropriately. Particularly, an epigenetic intervention would be ideal to define and fine-tune personalized precision medicine through pharmacoepigenomics in any specific biological process.

The epithelial-mesenchymal transition (EMT) is an essential process during embryogenesis (early embryonic development), as it promotes the conversion of static, boundary forming epithelial cells into multipotent tissue-generating mesenchymal cells.[1,2] For instance, the EMT is one of the central events occurring during vertebrate gastrulation that is a critical step in the establishment of body plan and organogenesis. On the one hand, the EMT process is also critical for wound healing and tissue regeneration in later adult stages.[2] On the other hand, pathologic activation of the EMT process during cancer progression can lead to metastasis.[3] EMT is typically characterized by the loss of cell-cell adhesion and apical-basal cell polarity, as well as the increased motility of cells, acquiring a mesenchymal phenotype and the ability to migrate and invade.[4] Recent evidence also suggests that cells that have passed through the EMT program also acquire stem cell properties.[4-6] Successful metastatic colonization is likely to be influenced by the capacity of cells to self-renew, and avoid or bypass apoptosis, as consequences of EMT, which subsequently allow cells to spawn malignant (ie, invasive and/or metastatic) growths.[7]

Several signaling pathways (eg, transforming growth factor β [TGF-β], Wnt, and Hedgehog signals) and transcription factors (eg, Snail, Twist, and Zeb) are well known to play essential roles in triggering the EMT process both during embryogenesis and in pathologic contexts.[8] Epigenetic modulations, such as DNA methylation and histone modification, are highly likely to be responsible for the EMT process because reversible alterations in gene activation and silencing with different cellular characteristics occur during EMT, and several pieces of evidence support the notion of transitional plasticity by epigenesis.[3,9]

We anticipate that by approaching the reciprocal state conversion in EMT, and in mesenchymal-epithelial transition (MET), previously uncharacterized developmental genes may be found to mediate the aging process and play a pivotal role in senescence. Conversely, unexplored senescence-related genes might also be involved in the early developmental process and its regulation. Presumably, the ease of epigenetic and epigenomic manipulation targeting the EMT program into an amenable model animal system will allow us to conduct an exhaustive exploration of novel genes/genotypes and epigenotypes that can be linked to the senescence phenotype, and thereby facilitate searching for the evolutionary and developmental origins of aging.

Here, to inspire the prospective view point of epigenetics and aging, we have overviewed some of the existing data on the effect and relationship of cellular senescence and the EMT process linked to organismal aging beyond the authentic developmental program, which highlight the existence of EMT regulators and their complex regulatory pathways and networks linked to epigenetics.

EMT VS MET IN DEVELOPMENT, CANCER, AND SENESCENCE

Both EMT and MET (EMT-MET) play crucial roles in the formation of the body plan and in the differentiation of multiple tissues and organs. Particularly, EMT also contributes to wound healing and tissue repair, but it can adversely cause organ fibrosis and promote carcinoma progression through a variety of mechanisms. EMT endows cells with migratory and invasive properties, induces stem cell properties, prevents senescence as well as apoptosis, and contributes to immunosuppression. Thus, the mesenchymal state is associated with the capacity of cells to migrate to distant organs and maintain "stemness," allowing their subsequent differentiation into multiple cell types during the development and initiation of metastasis.

Canonical cellular senescence has been argued as a cause (eg, for certain deleterious effects on the tissue microenvironment by a senescence-associated secretory phenotype [SASP]) or consequence (eg, by cellular stress or replication) of several pathophysiological responses in adults with advancing age. Thus, aging accompanies a decline and regression with various important homeostatic repercussions in tumor suppression and wound healing/tissue regeneration, where the physiological EMT process plays a gatekeeping role (Fig 1). Recent studies, however, reveal that senescence and apoptosis contribute to embryonic development in both pathologic and physiological contexts[10-16] suggesting a primordial essential role of senescence in organismal homeostasis beyond an authentic concept or dogma of its occurrence in advanced age.