Cell Interrupted — Modeling Epithelial to Mesenchymal Transition vs. Mitochondrial Dysfunction-Associated Senescence Tug of War

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Extended Abstract

Our bodies maintain tissue function by replacing injured cells and remaking disrupted structures, a process slowed by age. In injured epithelia, partial epithelial to mesenchymal transition (EMT) initiates migration toward sites of damage, followed by growth and reestablishment of the epithelium [1]. Partial EMT creates cells that can migrate as a collective by preserving their junctions. In contrast, full EMT allows them to break away and invade neighboring tissues, a process that aids tumor metastasis. At the same time, senescence makes short-term use of damaged cells by shutting down their ability to divide, but boosting survival, proliferation, and migration of neighbors [1]. Senescent cells trigger their own immune clearance, but their slow accumulation results in aging. Physiological senescence triggers such as reactive oxygen species cause mitochondrial dysfunction. The resulting energy deficit induces chronic oxidative stress and alters the secretome of senescent cells to interfere with their clearance; a state termed Mitochondrial Dysfunction-Associated Senescence (MiDAS) [2]. These cells impair healing in aging tissues and aid cancer evolution [3].

Despite substantial effort in modeling the regulatory networks of EMT and senescence, the two are typically studied in isolation. Here, we first offer a mechanistic molecular model for MiDAS in the form of a Boolean regulatory network that captures key aspects of mitochondrial dynamics during cell cycle progression. These include mitochondrial hyper-fusion at the G1/S boundary, mitochondrial fission in mitosis, and cell cycle errors when either process is blocked. Our model further captures mitochondrial fission and dysfunction during apoptosis and reversible hyperfusion under glucose starvation. Critically, we reproduce MiDAS observed in SIRT3-null cells and predict MiDAS in response to oxidative stress. We offer further predictions about the growth factor- and glucose-dependence of MiDAS and its reversibility at different stages of reactive oxygen species (ROS)-induced senescence.

Next, we link our MiDAS model to a large modular model of mechano-sensitive Epithelial to Mesenchymal Transition (EMT) and show that EMT is incompatible with MiDAS. Specifically, in contrast to healthy epithelial cells, those that have entered a MiDAS state are incapable of undergoing EMT in response to TGFβ (Fig. 1) or hypoxia. Conversely, cells that undergo EMT first are refractory to SIRT3- or oxidative stress-induced MiDAS. Intriguingly, mesenchymal cells under oxidative stress are predicted to undergo pyroptosis – explosive programmed cell death that releases intracellular contents into the environment rather than packaging the cell into non-inflammatory fragments. In summary, our models provide mechanistic insights into the relationship between oxidative stress-induced senescence and EMT and offers a foundation for building multiscale models of tissue aging.

Our work's ethical implications relate to its potential to reduce the environmental, monetary and time- costs of wet-lab experiments. Predictive models of the behavior of human cells and tissues are expected to become potent *in silico* counterparts to *in vitro* "organ-on-a-chips" [4], guiding experiments in cell biology and biomedical research. Such efforts can greatly reduce future use of animal models by anticipating complex tissue responses, drug side effects, the consequences of mutations, or non-intuitive crosstalk between seemingly unrelated

processes (e.g. senescence vs. EMT). That said, human "digital twins", or models matched to specific patients, will require careful considerations of privacy, informed consent, combating representation bias, and critically, harm from inaccurate predictions informing medical care.

References

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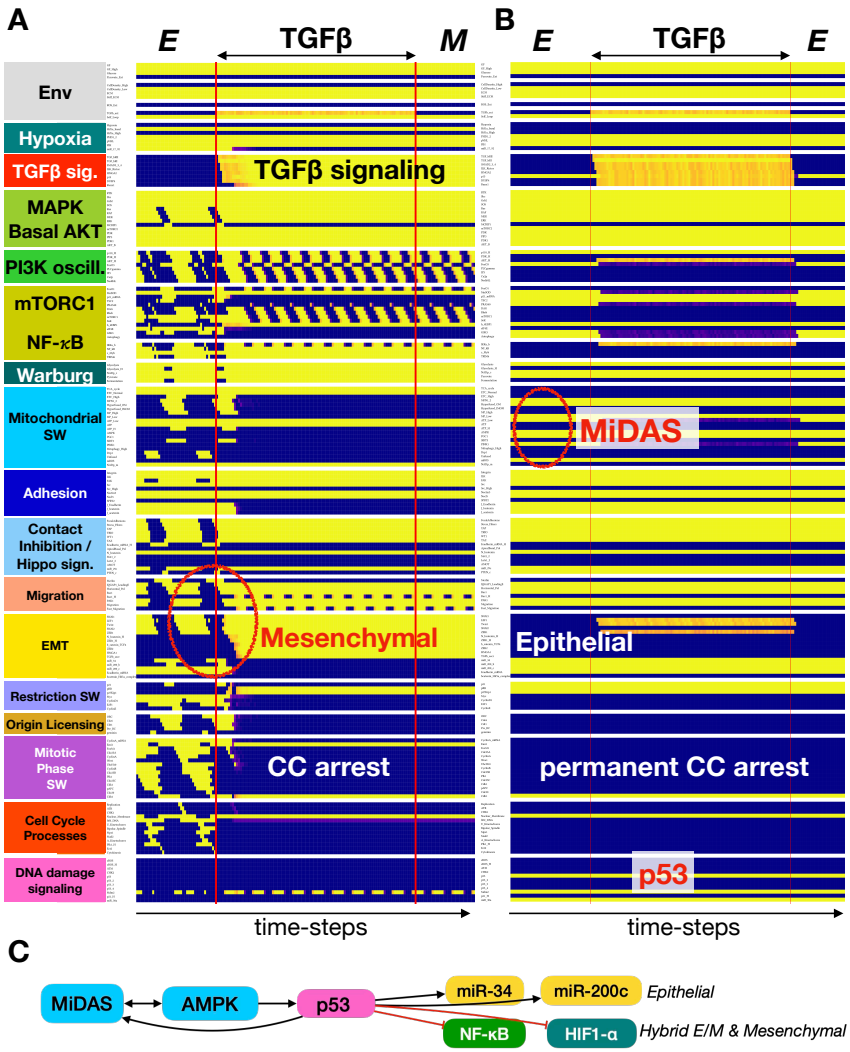

Figure 1. **MiDAS blocks TGFβ-induced EMT. A-B)** Dynamics of regulatory molecule activity during exposure of a dividing (A) or senescent epithelial cell to TGFβ for 100 update steps (75% ON). *X-axis:* Boolean time-steps; *y-axis*: nodes organized by regulatory modules; *yellow/dark blue*: ON/OFF; *vertical red lines*: start/end of signal; *red ovals*: key phenotypes or phenotype transitions. **C)** Mechanism responsible for lack of EMT in MiDAS cells: positive feedback maintaining MiDAS (*light blue*) with p53 (*pink*) upregulates epithelial microRNAs (*yellow*) and blocks EMT-promoting factors (*green/teal*).