Nicotinamide opposes glioblastoma cell aggressiveness by inducing senescence and correlated changes in histone marks

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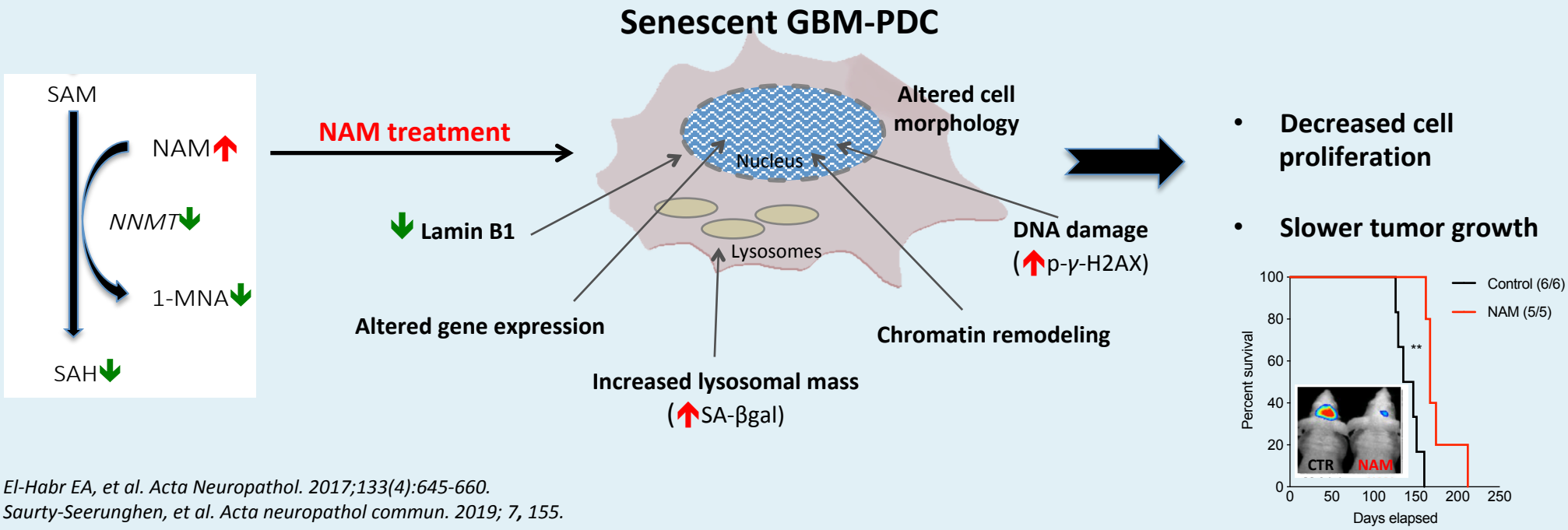
Glioblastoma (**GBM**), the most common and aggressive form of primary brain tumors in adults, are characterized by extensive intratumoral functional heterogeneity. Recently, the activity of metabolic enzymes has been shown to drive changes in cell functional states through modulation of the intracellular levels of specific metabolites[1,2]. These metabolites affect directly the activity of epigenetic modifiers and, as a consequence, changes in their intracellular levels can directly modulate gene expression. Here, we first observed that downregulation of the nicotinamide N-methyltransferase (**NNMT**) enzyme, known to favor GBM patient-derived cell (**GBM-PDC**) aggressiveness, is accompanied by increased levels of its substrate, **nicotinamide** (**NAM**). We then evaluated whether enhancing NAM intracellular levels suffices by itself to modulate GBM-PDC functional state. Accumulation of NAM within GBM-PDC induced their transition towards **senescence**. Senescent GBM-PDC exhibited features of normal senescent cells, including altered cell morphology, DNA damage, chromatin remodeling, increased lysosomal mass, decreased lamin B1 and reduced cell proliferation. NAM-induced senescence of GBM-PDC was accompanied by a global change in histone methylation and acetylation. Interestingly, transient NAM-treatment of GBM-PDC lowered their tumorigenic properties *in vivo*, resulting in better survival of xenografted mice. **Our results strengthen the emerging driver role of metabolism in the regulation of cell functional states.**



1. El-Habr EA, et al. Acta Neuropathol. 2017;133(4):645-660.
2. Saurty-Seerunghen, et al. Acta neuropathol commun. 2019; 7, 155.