TUSC2 Gene Therapy Activates a Transcriptional Program that Enhances Cellular Resilience to Aging-Associated Stress

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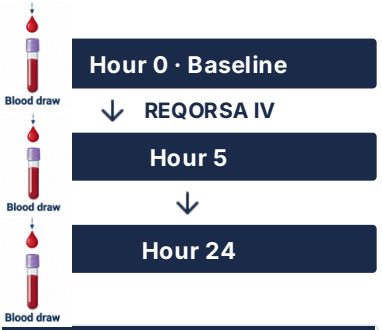
Background: Aging involves progressive mitochondrial dysfunction, proteotoxic stress, inflammation, and metabolic dysregulation. TUSC2, a regulator of mitochondrial calcium homeostasis, declines with age in human brain and other metabolically active tissues. Tusc2-deficient mice exhibit premature aging phenotypes, impaired stress tolerance, and reduced healthspan and lifespan. We investigated whether intravenous administration of quaratusugene ozeplasmid (quar oze), TUSC2-encoding plasmid lipoparticles, induces transcriptional changes consistent with enhanced cellular resilience in human tissues.

Methods: Whole-blood transcriptomes from 11 lung cancer patients enrolled in two clinical trials were analyzed before and 5 and 24 hours after intravenous quar oze administration. Differential gene expression and pathway analyses compared the 0–5-hour, 5–24-hour, and 0–24-hour **(Fig 1**) intervals to distinguish acute delivery-associated responses from delayed transcriptional remodeling.

Results: Quar oze induced a biphasic transcriptional response **(Fig.2)** At 5 hours, nucleic-acid sensing, interferon signaling, antiviral defense, chemokines, and innate immune pathways were strongly activated, consistent with an acute response to plasmid-containing lipoparticles (**Fig.3**). Between 5 and 24 hours, this response partially subsided, revealing a distinct transcriptional program. At 24 hours, sustained immune-surveillance and complement/phagocytic responses were accompanied by increased expression of genes involved in mitochondrial adaptation (PNPT1, SCO2, IDH1/2, YME1L1), autophagy and lysosomal function (LAMP3, STX17, AMBRA1, CTSL), and endoplasmic-reticulum proteostasis (CALR, PDIA3, EDEM1, DNAJA1, ATF5). **(Fig.4)** Concurrently, ribosomal, translational, and IGF/mTOR-associated growth programs were suppressed.

STUDY DESIGN & OVERVIEW

Quaratusugene ozeplasmid delivers the ***TUSC2/FUS1*** tumor suppressor via lipid nanoparticle IV. Whole-blood RNA-seq captures the systemic host transcriptional response.



Comparison	UP	DOWN
H0→H5	4,540	5,585
H5→H24	3,264	3,783
Net H0→H24	2,345	1,949

FIGURE 1

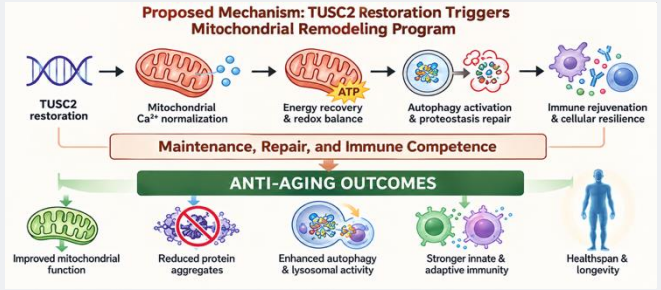


FIGURE 5

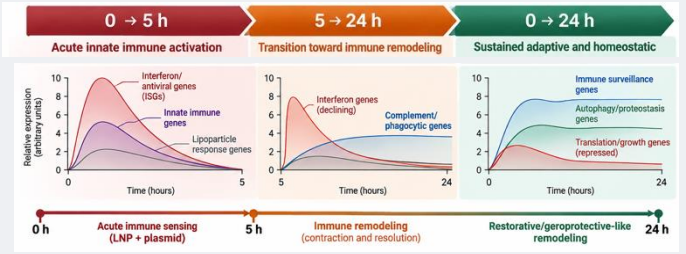


FIGURE 2

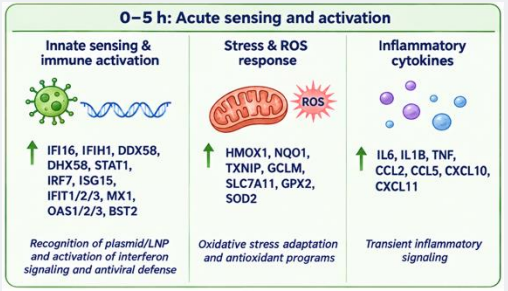


FIGURE 3

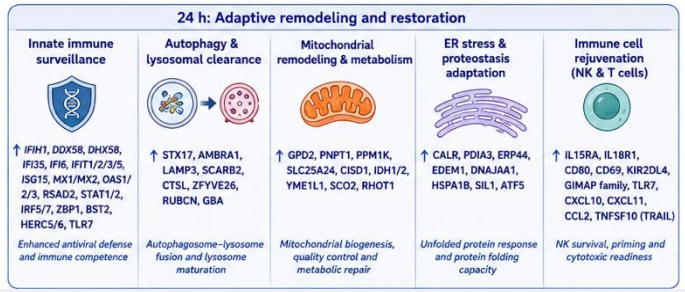


FIGURE 4

CONCLUSIONS

- Quaratusugene ozeplasmid triggers a rapid, broad transcriptional response within 5 h, dominated by innate immune activation (***CXCL10*** 488x, ***IFIT2*** 78x, ***IL1RN*** 49x) and calcium/CAMK pathway induction
- The autophagy-lysosomal axis is strongly induced at Hour 5 and remains elevated at Hour 24 (***LAMP3*** 118x, ***USP18*** 85x), consistent with TUSC2-driven selective autophagy
- Mitochondrial OXPHOS genes are transiently suppressed at Hour 5 (166 genes DOWN) then strongly recover by Hour 24, with ***PPARGC1B*** (biogenesis master regulator) rebounding 11x — suggesting metabolic reprogramming toward oxidative metabolism
- At 24 h there was a strong shift to adaptive remodeling – autophagy, mitochondrial repair, proteostasis, and immune rejuvenation. Moreover, translation and growth pathways (mTOR/IGF, ribosomes) were suppressed

Overall, response to quaratusugene ozeplasmid resembles conserved longevity mechanisms (mitohormesis, maintenance overgrowth) (FIG 4 & 5)