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Extracellular vesicles from aged individuals trigger mitochondrial dysfunction in haematopoietic progenitor cells

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Letter to the Editor

The role of extracellular vesicles (EVs) in haematopoietic stem cell (HSC) ageing remains poorly explored. We have collected evidence to suggest that EVs from older human individuals significantly alter the proteome and transcriptome of haematopoietic progenitor cells (HPCs) and specifically impair mitochondrial activity. This work implies that EVs contribute to the decline of HPC functionality during ageing, which we propose creates a vulnerability for age-based blood disease development.

Ageing alters haematopoietic stem and progenitor cell (HSPC) biology, leading to the decline of blood and immune cell function. Significant strides have been made understanding cell autonomous factors during HSPC ageing, namely genetic and epigenetic alterations, decreased quiescence, impaired autophagy and mitochondrial dysregulation[1]. With the identification of clonal haematopoiesis (CH) and its associated risk of progression to myeloid neoplasms, concerted effort has been made toward being able to accurately predict risk and develop therapeutic approaches to avert/delay progression of CH. Recently, three publications identify mitochondrial metabolism as a central target in HSPCs with mutated DNMT3a, suggesting that during ageing, CH clones commandeer the mitochondria, leading to an enhancement of oxidative phosphorylation[2-4]. Questions remain as to what cellular conditions exist that make cells permissive to CH mutation interactions.

Mitochondria are the quintessential metabolic hubs that coordinate energy production via oxidative phosphorylation with a network of biosynthetic pathways critical for cell biomass production. These primary functions are further interlinked with the regulation of apoptosis and redox balance, which altogether control activation of homeostatic signalling pathways and ultimately overall cell survival[5]. Mitochondrial dysfunction is one of the ageing hallmarks[6] and is commonly accepted to be essential in leukaemogenesis, to support the increased metabolic needs in rapidly proliferating transformed leukaemic stem cells[1]. Notably, the majority of studies investigating mitochondria, ageing and cancer have primarily focused on cell intrinsic factors[8], and less on the external factors present in the pre/leukaemic microenvironment.

Extracellular vesicles have emerged as critical mediators of cell-to-cell communication. These nano-sized (30nm -10 microns) phospholipid-enclosed particles are secreted by cells which mediate intercellular communication through the transfer of proteins, lipids, and nucleic acids. In blood cancers, tumour-derived EVs are well documented to remodel the bone marrow microenvironment, suppressing normal haematopoiesis and promoting leukaemic expansion[9,10]. Additionally, EVs are being explored for their therapeutic potential as disease biomarkers due to their ability to mirror the physiological or pathological state of their cells of origin. Although few studies have explicitly examined connections between EVs and HSPC ageing, some evidence suggests an age-based decline in functional mitochondria in multiple subpopulations of plasma EVs[11].

Our previous work demonstrates that ageing alters blood EV content[12], thereby having the potential to contribute to HSPC dysfunction[13]. To expressly investigate exactly how blood EVs affect HSPCs in the context of ageing, plasma-derived EVs were enriched from young (20 – 40 years), middle (40 – 60 years), and older (60 – 85 years) human subjects. EV purification and characterization methods were based on guidelines from the Society of Extracellular Vesicles[14]. Post enrichment, EVs were incubated with umbilical sourced $CD34^+$ cells for 48hrs, with cells subsequently washed with PBS and prepared for proteomics (Fig 1a). When comparing the differential expression of bulk proteins compared to PBS control samples, Volcano plots suggested a progressive increase in the number of differentially expressed proteins following exposure to EVs from individuals as they age (Fig.1b). Using proteins (n=1916 proteins identified after pre-processing and duplicate removal) identified in the mass spectrometry data, we implemented the ActivePathways algorithm as a means to perform integrative pathway enrichment analysis for significant biological processes triggered by EVs. The resulting enrichment map of biological pathways reveals that only EVs from older subjects significantly alter the proteome of HSPCs (Fig.1c). EVs from older subjects were observed to trigger pathways involved in translation, cellular response to stress/stimuli, ribosomal RNA processing, nonsense mediated decay and regulation of mitochondrial membrane potential (Fig.1c). Few to no biological processes were triggered in the presence of EVs from either young or middle-aged subjects. Ingenuity pathway analyses (IPA) further supported enrichment of the select processes similar to ActivePathways, and additionally provided directionality of pathway (i.e. activation or inhibition) based on z-score (Fig.2a), supporting a predicted activation of eukaryotic translation initiation (z-score= 6.856; adj-pval= 1.84E-05), eukaryotic initiation factor 2 (EIF2) signalling (z-score= 4.082; adj-pval= 2.31E-05), major pathway of rRNA processing in the nucleolus and cytosol (z-score= 3.807; adj-pval= 1.56E-04), and nonsense-mediated decay (NMD) (z-score= 3.807; adj-pval= 1.56E-04)(Fig. 2a,b). Thus, EVs from older individuals are altering normal physiological processes.

To investigate how EVs might regulate specific HSPC populations at a transcriptional level, single-cell transcriptome analyses was employed (as outlined in Fig.1a) (n=3 biological EV samples per group). Cell type annotation of the heterogeneous HSPC population was performed using normalized gene expression of top differentially expressed and key cell lineage marker genes, identifying 14 unique haematopoietic cell subsets. Uniform Manifold Approximation and Projection (UMAP) display the 14 distinct HSPC subtypes based on their transcriptomic profiles (Fig. 2b).

Despite the proportion of the 14 haematopoietic cell types remaining unchanged post 48h incubation with plasma-derived EVs from young, middle-aged and older individuals compared to control (Fig.2c), a disproportionate number of differentially expressed genes (DEGs) were identified depending on both the cell type and the donor age of EVs (Fig. 2d). Interestingly, the MPP population and downstream myeloid precursor cells displayed the highest number of DEGs

(Fig. 2d). The MPP cell subset (representing 30.9 – 31.4% of identified cells following EV exposure was the most transcriptionally sensitive out of the 14 HSPC populations to EV exposure (Fig.2e). Results suggests that while EVs from different aged subjects affect a similar number of genes, the magnitude and significance of these changes is more pronounced in response to exposure to EVs derived from older individuals. We continued our analysis on HSC, MPP, MPP3, MEMP, CMP, MEP, GMP, neutrophils, monocytes, and eosinophils, based on these populations possessing a sufficient number of DEGs.

Our analyses revealed 178 altered biological functions that were significantly perturbed following exposure to EVs of older individuals using Benjamini-Hochberg corrected p-value of <0.05 compared to EVs from young and middle-aged subjects (Suppl. Table 1). The greatest number of biological functions generally fell into three categories: translation, mitochondrial regulation and cell cycle progression. Based on significance (z-score) and literature, interrogation into mitochondria regulation was further pursued. What was most interesting was that, similar to the proteomic data, only EVs from older individuals significantly abrogated signalling pathways, in contrast to young and middle-age sourced EVs, which altered few/no pathways (Fig. 3b).

Transcriptomic data revealed that EVs from older individuals had significant impact on physiological pathways such as respiratory electron transport, oxidative phosphorylation, complex 1 biogenesis, mitochondrial translation and degradation (Fig. 3a). In addition, this effect was most profound on MPPs, MEMPs, CMPs and neutrophils. As a result. mitochondrial dysfunction was predicted to be the most perturbed canonical pathway in MPP, MEMP, CMP, and neutrophil cell populations as denoted by the highest activated z-score among all other biological processes present in each of the above-mentioned cell types. To confirm our pathway analyses, we decided to functionally assess the mitochondrial membrane potential ($\Delta\Psi m$) of umbilical cord sourced $CD34^{+}CD38^{-}$ cells (n=4), incubated with EVs from young, middle and older sourced EVs (n=6 per age group). Following a 48hr incubation as previously completed, Tetramethylrhodamine, methyl ester (TMRM) staining was performed and assessed using flow cytometry. In Fig. 3b, results demonstrate that blood EVs compromise mitochondrial function in an age-dependent manner, confirming our bioinformatic analyses. Considering the MPP cell type comprises a large portion of all cells analysed and was the most primitive haematopoietic population identified, being upstream of the MEMPs, CMPs and neutrophils, we further probed the genes responsible for the predicted mitochondrial dysfunction. All genes captured in our transcriptomic dataset involved in mitochondrial regulation are indicated in Fig. 3c, with downregulated genes in green, upregulated genes in red, and implied regulators in orange (upregulated) and blue (downregulated). Based on genes affected, 4 out of 5 Complexes within the Electron Transport Chain were impacted by the exposure of EVs from older individuals. Taking a more global approach, we utilized the molecule activity predictor (MAP) function of IPA, to identify key regulators and identified peroxisome proliferator-activated receptor gamma

coactivator 1-alpha (PPARGC1A, commonly known as PGC-1α) as a central regulator (Fig. 3d) that was predicted to be downregulated. These data suggest EVs from older individuals de-regulates mitochondrial function at the single-cell level in both primitive and progenitor haematopoietic cells. Interestingly, another study performing reciprocal studies[15] shows PGC-1α is not only downregulated in older mice, but also that injected EVs from young mice stimulate PGC-1α, complementing our own observations of EVs from older humans dampening PGC-1α.

In conclusion, we have collected evidence to suggest that blood EVs from older human individuals significantly alter the proteome and transcriptome of HPCs when compared to EVs from younger individuals, corroborating results that blood sourced EVs have little effect on the most primitive HSC population[15]. Importantly, EVs from older individuals initiate differential expression of genes in primitive multipotent and myeloid progenitors, and upregulate mitochondrial dysfunction, specifically dampening peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) activity, a critical modulator in energy metabolism and mitochondrial biogenesis. Our work suggests that as individuals age, EVs that are released into the bloodstream are detrimental to HPC function and specifically impair mitochondrial activity. This work implies that blood EVs contribute to the decline of HPC functionality and may preclude age-based disease development.

Human sample collection followed the Declaration of Helsinki and was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB). Approval for the collection of human umbilical cord blood was obtained prior to commencement of the study (Department Code; DBMS-093-18, TRAQ# 6024642). Informed verbal consent was obtained from all blood donors undergoing total hip arthroplasty surgery according to HSREB regulations.

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Figure Legends

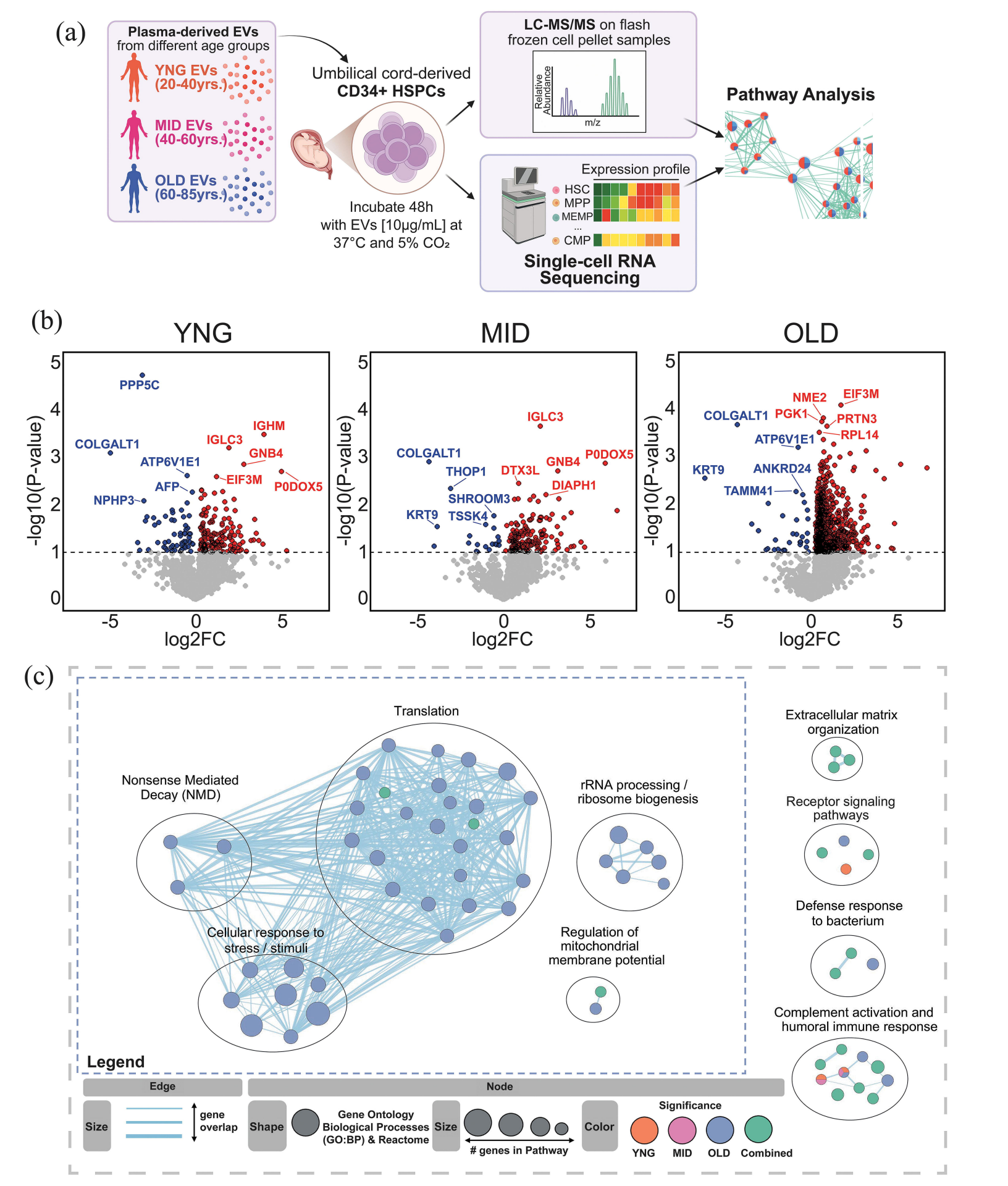
Figure 1. EVs from older individuals alter the expression of various biological processes in the proteome of HSPCs. CD34+ cells were incubated for 48h with or without EVs from various age groups (PBS control; young 20 – 40 years; middle-aged 40 – 60 years; old 60 – 85 years). (a) Schematic of experimental design for proteomics and single cell transcriptomics. (b) Volcano plots comparing HSPC protein post 48hr EV incubation. (c) Enrichment map of biological processes (Gene Ontology) and molecular pathways. Reactome for each EV age group compared to control (FDR <0.05). Circled areas indicate common biological themes. Statistical analysis: Unpaired t-test with Welch correction.

Figure 2. EVs from differing age groups alter the proteome and transcriptome of HSPCs. CD34+ cells were incubated for 48h with or without EVs from various age groups (PBS control; young 20 – 40 years; middle-aged 40 – 60 years; old 60 – 85 years). (a) Ingenuity Pathway Analysis (IPA) predicted canonical pathways enriched (Benjamini-Hochberg FDR < 0.05) in the proteome. Bar plots show z-scores of enriched functions (red: activated, z-score ≥ 2; blue: inhibited, z-score ≤ -2). (b) Single cell transcriptional analyses: Uniform manifold approximation and projection (UMAP) visualization of full dataset (n=106,267 cells) clustered into n=14 HSPC subtypes. namely haematopoietic stem cell (HSC), multipotent progenitor (MPP), myeloid-biased multipotent progenitor (MPP3), megakaryocyte-erythroid-mast cell progenitor (MEMP), common myeloid progenitor (CMP), megakaryocyte-erythroid progenitor (MEP), granulocyte-monocyte progenitor (GMP), neutrophil (Neutro), dendritic cell (DC), monocyte (Mono), eosinophil (Eosin), mast cell (Mast), lymphoid-primed multipotent progenitor/B cell (LMPP/B), common lymphoid progenitor (CLP). (c) Bar plot showing the cell lineage proportions per sample. (d) Bar plot differentially expressed genes (DEGs) in specific cell types, after multiple testing correction (Benjamini-Hochberg FDR < 0.05) compared to control. (e) Volcano plots representing DEGs (Bonferroni adjusted p-value < 0.05) in MPP cell subtypes following exposure to EVs as indicated.

Figure 3 . EVs from older subjects augment mitochondrial dysfunction in MPPs and downstream progenitors. (a) Mitochondrial-related pathways significantly modulated in screen. Dot plots separated by EV exposure (young=pink; mid=orange; old=blue) displaying altered canonical pathways. Activated pathways (z-score ≥ 2) or inhibited pathways (z-score ≤ -2). All highlighted pathways significant (Benjamin-Hochberg FDR < 0.05). The dot size represents the negative log p-value. (b) TMRM staining of $CD34^{+}CD38^{-}$ cells post EV incubation (representative plot and averaged data from n=4 HSPC and n=6 EV samples). Statistical Analysis: RM one-way ANOVA, with Holm-Šídák's multiple comparisons test * P ≤ 0.05, ** P ≤ 0.01 (c) Mitochondrial genes identified in MPPs treated with EVs from older subjects. Upregulated genes indicated in red, downregulated in green, predicted activation in orange, predicted inhibition in blue. Please note that differing color of print have no other meaning than making them easier to read (d) the predicted inhibition of PPARGC1A (PGC-1α), a crucial

regulator of mitochondrial regulation. Pathway analyses performed using Ingenuity Pathway Analysis (IPA) (Benjamin-Hochberg FDR < 0.05).

Online Supplementary Table provide as Excel file.


(a)
Plasma-derived EVs
from different age groups
YNG EVs
(20-40yrs.)
MID EVs
(40-60yrs.)
OLD EVs
(60-85yrs.)
Umbilical cord-derived
CD34+ HSPCs
Incubate 48h
with EVs [10µg/mL] at
37°C and 5% CO2
LC-MS/MS on flash
frozen cell pellet samples
Relative Abundance
m/z
Expression profile
HSC
MPP
MEMP
...
CMP
Single-cell RNA
Sequencing
Pathway Analysis
(b)
YNG
MID
OLD
-log10(P-value)
log2FC
PPP5C
COLGALT1
IGHM
IGLC3
GNB4
ATP6V1E1
EIF3M
P0DOX5
AFP
NPHP3
IGLC3
COLGALT1
GNB4
P0DOX5
THOP1
DTX3L
DIAPH1
SHROOM3
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TSSK4
NME2
EIF3M
COLGALT1
PGK1
PRTN3
RPL14
ATP6V1E1
KRT9
ANKRD24
TAMM41
(c)
Translation
Nonsense Mediated
Decay (NMD)
rRNA processing /
ribosome biogenesis
Cellular response to
stress / stimuli
Regulation of
mitochondrial
membrane potential
Extracellular matrix
organization
Receptor signaling
pathways
Defense response
to bacterium
Complement activation and
humoral immune response
Legend
Edge
Size
gene
overlap
Node
Shape
Gene Ontology
Biological Processes
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Size
genes in Pathway
Color
Significance
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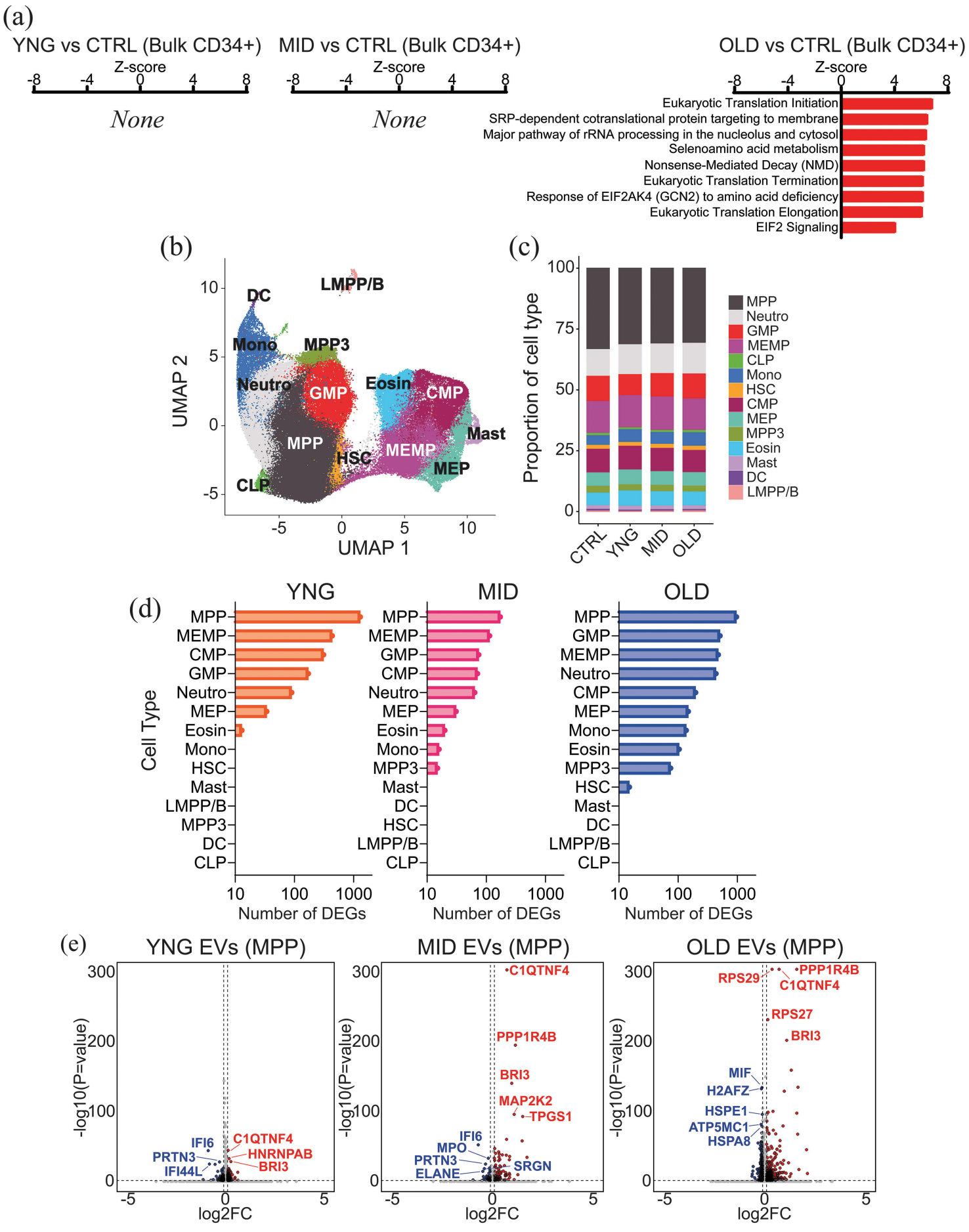
MID
OLD
Combined


(a)
YNG vs CTRL (Bulk CD34+)
Z-score
-8 -4 0 4 8
None
MID vs CTRL (Bulk CD34+)
Z-score
-8 -4 0 4 8
None
OLD vs CTRL (Bulk CD34+)
Z-score
-8 -4 0 4 8
Eukaryotic Translation Initiation
SRP-dependent cotranslational protein targeting to membrane
Major pathway of rRNA processing in the nucleolus and cytosol
Selenoamino acid metabolism
Nonsense-Mediated Decay (NMD)
Eukaryotic Translation Termination
Response of EIF2AK4 (GCN2) to amino acid deficiency
Eukaryotic Translation Elongation
EIF2 Signaling
(b)
DC
LMPP/B
Mono
MPP3
Neutro
GMP
Eosin
CMP
Mast
MPP
HSC
MEMP
MEP
CLP
UMAP 2
UMAP 1
(c)
Proportion of cell type
CTRL
YNG
MID
OLD
MPP
Neutro
GMP
MEMP
CLP
Mono
HSC
CMP
MEP
MPP3
Eosin
Mast
DC
LMPP/B
(d)
YNG
MID
OLD
Cell Type
Number of DEGs
(e)
YNG EVs (MPP)
MID EVs (MPP)
OLD EVs (MPP)
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log2FC
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PRTN3
IFI44L
C1QTNF4
HNRNPAB
BRI3
MPO
ELANE
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HSPE1
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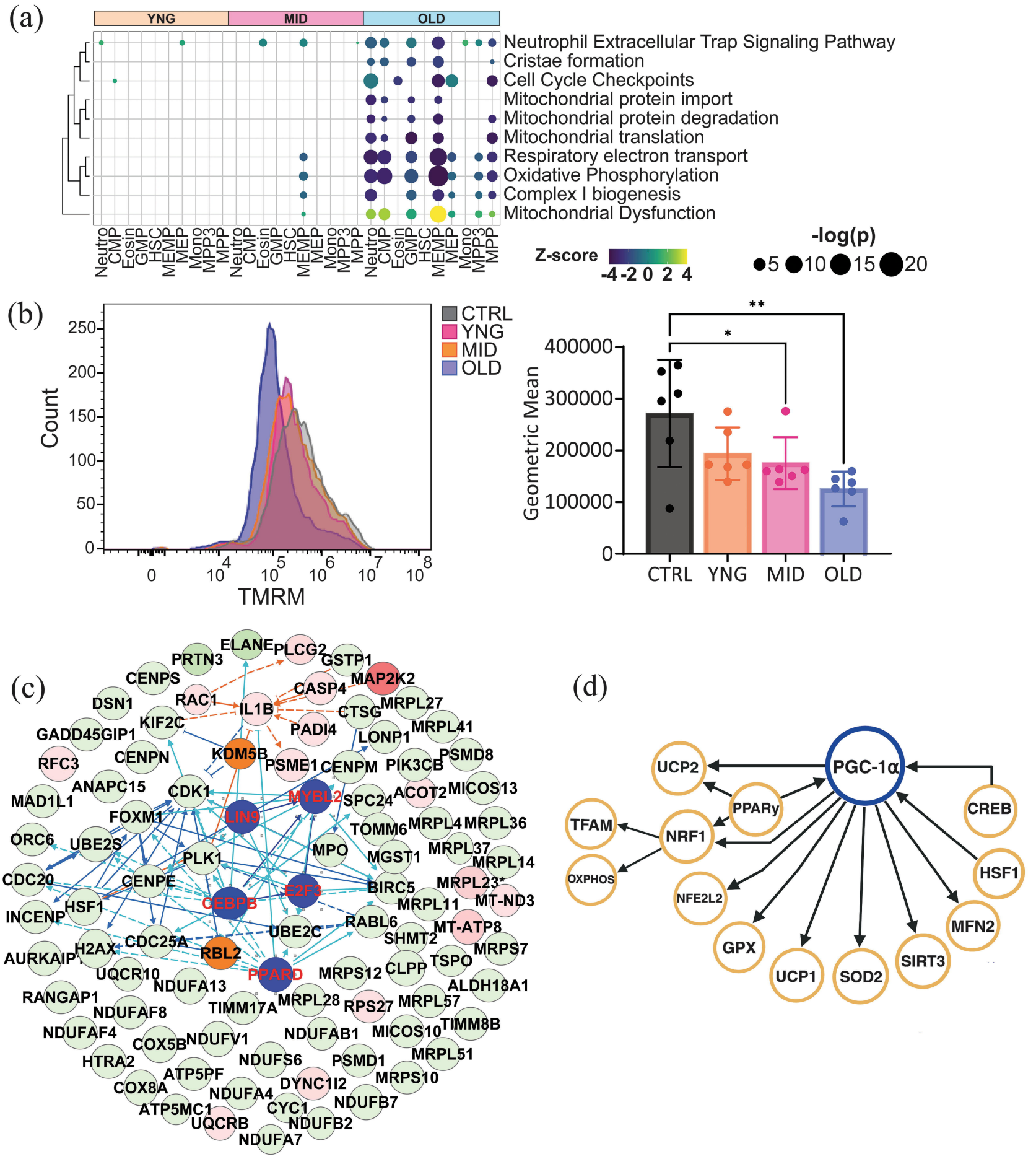
(a)
YNG
MID
OLD
Neutrophil Extracellular Trap Signaling Pathway
Cristae formation
Cell Cycle Checkpoints
Mitochondrial protein import
Mitochondrial protein degradation
Mitochondrial translation
Respiratory electron transport
Oxidative Phosphorylation
Complex I biogenesis
Mitochondrial Dysfunction
Neutro
CMP
Eosin
GMP
HSC
MEMP
MEP
Mono
MPP3
MPP
Z-score
-4 -2 0 2 4
-log(p)
5 10 15 20
(b)
CTRL
YNG
MID
OLD
Count
TMRM
Geometric Mean
CTRL YNG MID OLD
(c)
ELANE
PLCG2
GSTP1
PRTN3
CENPS
MAP2K2
CASP4
DSN1
RAC1
IL1B
CTSG
MRPL27
KIF2C
PADI4
LONP1
MRPL41
GADD45GIP1
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CENPM
PIK3CB
PSMD8
RFC3
CENPN
ANAPC15
CDK1
MYBL2
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MICOS13
MAD1L1
FOXM1
LIN9
TOMM6
MRPL4
MRPL36
ORC6
UBE2S
PLK1
MPO
MGST1
MRPL37
MRPL14
CDC20
CENPE
E2F3
BIRC5
MRPL23*
HSF1
CEBPB
MRPL11
MT-ND3
INCENP
RABL6
UBE2C
MT-ATP8
SHMT2
H2AX
CDC25A
MRPS7
AURKAIP1
RBL2
TSPO
UQCR10
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HTRA2
NDUFS6
PSMD1
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ATP5PF
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COX8A
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NDUFA4
NDUFB7
ATP5MC1
CYC1
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GPX
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SOD2
SIRT3