Impact of donor age and glucocorticoid exposure on receptor balance and metabolism in human bone marrow mesenchymal stromal cells

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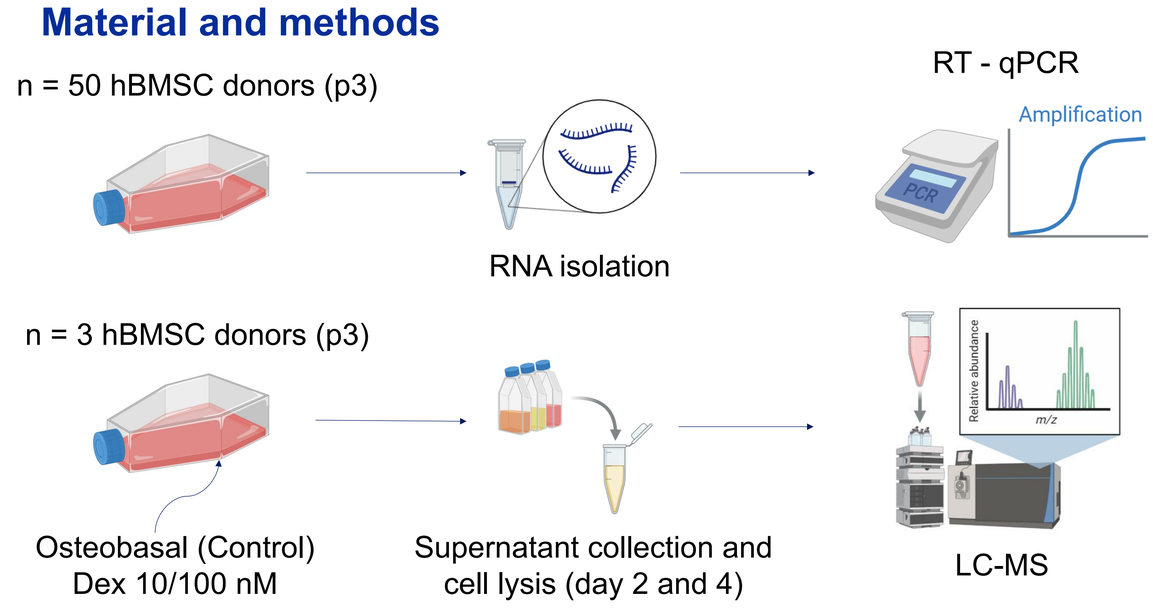
Background

- Glucocorticoids (GCs) are widely used anti-inflammatory drugs, but long-term treatment is a major cause of secondary osteoporosis.
- Underlying mechanisms are not fully understood, particularly in human bone marrow-derived mesenchymal stromal cells (hBMSCs).
- GCs activate both the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR).
- MR signalling has been implicated in GC-induced bone loss, but its specific role remains poorly defined.

Aims

- Understand the basal differences in hBMSCs between GR (*NR3C1*) and MR (*NR3C2*) gene expression levels.
- Analyse the metabolite footprint of hBMSCs treated with dexamethasone.

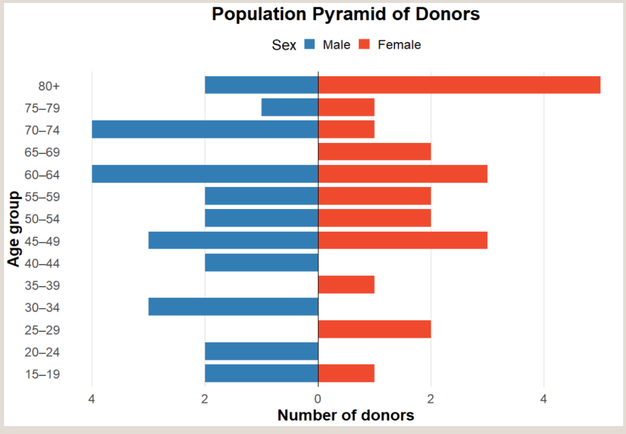
Material and methods



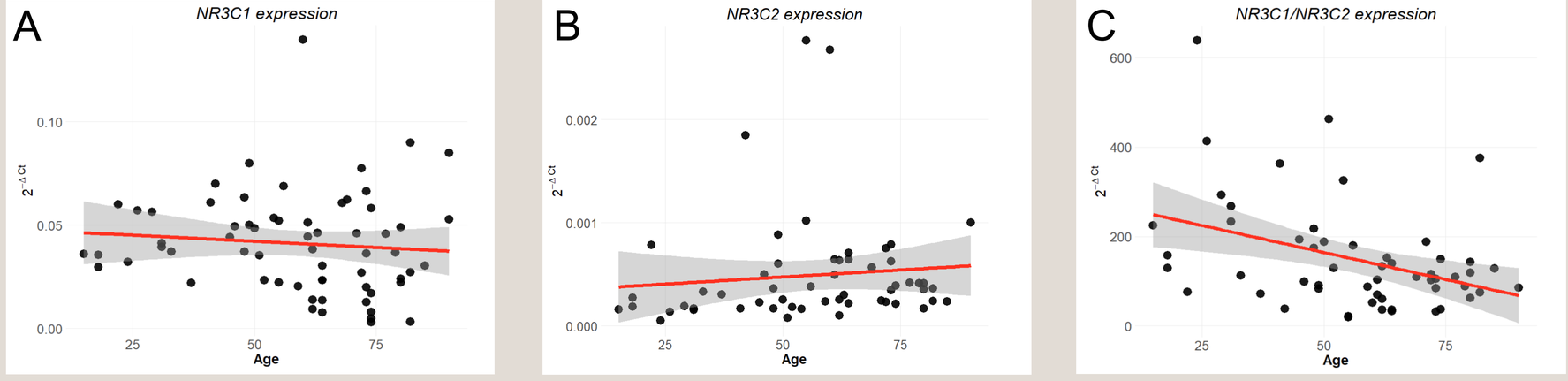
Results

Basal expression of *NR3C1* and *NR3C2* in human BMSCs

- Spearman correlation was used for all tests due to non-normal data distribution.
- *NR3C1* gene expression did not show any correlation with age nor gender in expanded hBMSCs.
- *NR3C2* gene expression positively correlated with donor age (Rho = 0.2861, p-value = 0.03419).
- The *NR3C1*/*NR3C2* ratio showed a negative correlation (Rho = - 0.3415, p-value = 0.0107).



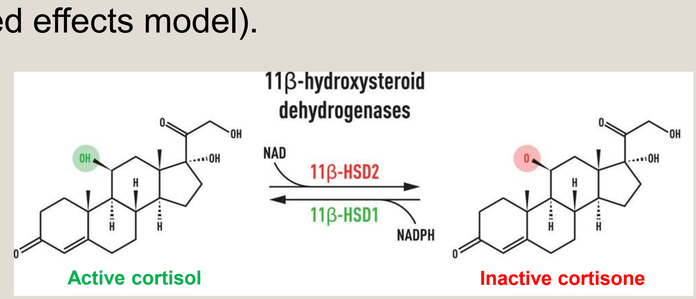
Population distribution of n=50 BMSC donors used in the basal expression analysis



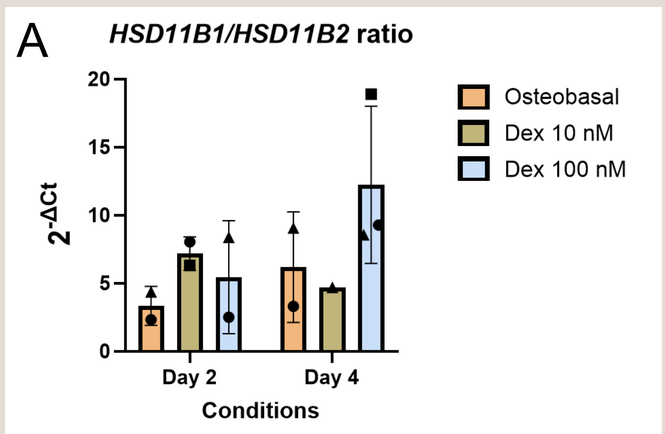
Scatter plots showing the expression of *NR3C1* (A), *NR3C2* (B), and *NR3C1/NR3C2* ratio (C) in relation to donor age.

Effect of dexamethasone on receptor expression and GC metabolism

- Dexamethasone slightly increased *HSD11B1*/*HSD11B2* ratio (especially at day 4, 100 nM).
- *NR3C1*/*NR3C2* ratio tends to be increased by dexamethasone in comparison to the osteobasal control.
- Trends observed but not statistically significant (two-way mixed effects model).



Schematic of HSD11B1 and HSD11B2 enzyme reactions



***HSD11B1*/*HSD11B2* (A) and *NR3C1*/*NR3C2* (B) gene expression ratio at days 2 and 4 in osteobasal, dexamethasone 10 nM and 100 nM conditions.**
Donor characteristics:
Square: Female, 62 years old.
Triangle: Female, 87 years old.
Circle: Male, 86 years old,.

Discussion

- qPCR results from monolayer-expanded hBMSCs indicate that **MR expression increases with donor age**, shifting the GR/MR balance and potentially **sensitizing hBMSCs** to detrimental effects of glucocorticoids, in agreement with previous observations in mice (Shaver et al. ORS2024 abstract - Mineralocorticoid receptor inhibition mildly blunts age-dependent decline in vertebral bone in female C57BL/6 mice).
- **Dexamethasone** tends to **increase the *HSD11B1*/*HSD11B2* ratio** therefore potentially reducing its own degradation.
- **NR3C1/NR3C2 ratio** tends to **increase** in **dexamethasone-treated hBMSCs**, though both receptors are downregulated.
- LC-MS analysis still pending (metabolite and steroid panels). Validations at the protein levels to be performed.
- Overall, these findings may represent a first step towards understanding **how GR and MR signalling is modulated by age** and metabolic variations with **glucocorticoid exposure**.

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