ageing mechanisms, diagnosis/prognosis of age-related disease and even novel treatment targets.

Objectives: To quantify relationships between circulating microRNA expression and biological ageing and determine whether microRNAs may be a molecular clock.

Methods: This pilot work is a nested substudy within a prospective, longitudinal birth cohort from May/June 1947 (the Newcastle Thousand Families Study NTFS). Serum samples from 23 subjects taken at ages 50 and 62 years were extracted from the biobank. HTG EdgeSeq microRNA whole transcriptome assay was performed, measuring expression of 2083 human microRNA transcripts using an array followed by next generation sequencing. Global microRNA expression profiles were generated and analysed using this technology, profiling all known microRNAs from a small volume of serum (<15 µL). NIHR funding has been secured for whole cohort analysis.

Results: Resulting data has shown very strong associations (up to $p < 10^{-12}$) for biological ageing, with 84 microRNAs meeting p -values < 0.05 (see heat map). Analysing the whole cohort will independently validate and extend the findings, in order to identify an ageing signature; the molecular clock.

Conclusions: This study suggests very strong changes in microRNAs in individuals between 50 and 62, suggesting microRNA signature is a molecular clock. These observations need to be confirmed and extended to validate serum microRNAs as biomarkers for ageing, for early detection of age-related disease and as tools to monitor ageing trajectory.

REFERENCES:

- [1] Hatse S, et al. Circulating MicroRNAs as Easy-to-Measure Aging Biomarkers in Older Breast Cancer Patients: Correlation with Chronological Age but Not with Fitness/Frailty Status. *PLoS ONE* 2014;9(10):e110644.
- [2] Zhang H, et al. Investigation of microRNA expression in human serum during the aging process. *J Gerontol A Biol Sci Med Sci*. 2015;70(1):1–2–9.
- [3] Ameling S, et al. Associations of circulating plasma microRNAs with age, body mass index and sex in a population-based study. *BMC Med Genomics* 2015;8:61.

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THU0020

TOCILIZUMAB DECREASES THE PRO-INFLAMMATORY ROLE OF PLATELETS IN RHEUMATOID ARTHRITIS: IDENTIFICATION OF A NEW MECHANISM OF ACTION ASSOCIATED WITH POSITIVE RESPONSE?

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Background: Tocilizumab (TCZ), a humanised monoclonal antibody directed against IL-6 receptor, is an efficient treatment for rheumatoid arthritis (RA) but its mechanisms of action are not yet well understood.

Objectives: To identify new mechanisms of action of TCZ, by the study of gene expression fluctuations, between baseline (BL) and 3 months of treatment (T_{3m}), in RA patients.

Methods: TOSCA study has been realised to evaluate efficiency and tolerance of TCZ administered subcutaneously in active RA patients. Among the 125 patients of TOSCA study, 38 were ranked according to their treatment response after 3 months: 29 good responders (GR), 19 of which were also treated by methotrexate (MTX) and 10 non responders (NR), 7 of which were treated by MTX (GR: DAS 28-ESR_{3m} < 3.2 and Delta DAS28-ESR_(BL-3m) ≥ 3; NR: DAS 28-ESR > 3.2 and Delta DAS28-ESR_(BL-3m) < 3). A transcriptomic analysis was performed using a 44K whole human genomic DNA microarray (Agilent) on whole blood cells collected at BL and at T_{3m}. We identified genes with statistically significant expression fluctuations between BL and T_{3m} specifically in GR group (and not in NR group), treated by TCZ in monotherapy (excluding genes which fluctuated only with the association TCZ-MTX). Functional bio-informatics analysis was applied to this set of transcripts, by interrogation of Gene Ontology database, using Single Experiment Analysis tool and Natural Language Processing algorithms.

Results: Overall, 1089 transcripts significantly dysregulated were identified only in GR group at T_{3m} (t test, $p < 0.05$). This first set of transcripts was reduced to 783 by exclusion of transcripts that were fluctuated specifically when MTX was associated with TCZ in GR group. The functional analysis with these 783 genes dysregulated under TCZ in monotherapy enabled the identification of 8 transcripts (*CLU*, *F13A1*, *ITGA2B*, *ITGB3*, *SELP*, *SNCA*, *SPARC*, *TREML1*) whose relative abundances were significantly reduced at T_{3m}. These genes were enriched in "platelet alpha granule" GO functional category. Proteins encoded by these genes, either released in blood circulation or expressed at the cell membrane in case of platelet activation, have a pro-inflammatory activity through an interaction between platelets and immune cells.

Conclusions: This transcriptomic analysis suggests a new mechanism of action of TCZ in RA and the importance of platelets activation in RA pathophysiology. Indeed, genes linked with the pro-inflammatory role of platelets were down regulated. Further functional studies will be necessary to validate the direct effect of TCZ on platelets in RA.

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THU0021

DIFFERENTIAL EFFECTS OF TR14 VERSUS DICLOFENAC ON COX/LOX PATHWAYS REVEALED BY RNASEQ

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Background: Anti-inflammatory agents are used widely in treating numerous pain and inflammatory conditions. With a focus on the COX/LOX pathways in cutaneous wound repair in mice, the therapeutic activities of Tr14 (Traumeel), a multicomponent/multitarget natural product, and diclofenac (NSAID), a non-selective cyclooxygenase (COX) inhibitor were compared. The COX enzymes convert arachidonic acid into prostaglandins and thromboxanes, while the lipoxygenase (LOX) pathway generates more pro-inflammatory leukotrienes. Differential effects were identified via transcriptome analysis (RNAseq).

Objectives: To compare the transcriptomic changes after administration of Tr14 or diclofenac in a mouse cutaneous wound healing model, with particular emphasis on the COX/LOX pathway.

Methods: After abrasive wounding, the wounds were treated with topical Tr14 (34 mg/ml) in combination with subcutaneous Tr14 injections (9.5 mg/ml), or with subcutaneous Tr14 injections only, or topical diclofenac at clinically relevant doses (2 mg/ml). Skin samples were analysed for RNA transcript profiling by RNAseq at specific times (12 hour, 24 hour, 36 hour, 72 hour, 96 hour, 120 hour, 192 hour) after injury. Differentially expressed genes (DEGs) were computed at each time point between diclofenac vs control or Tr14 vs control, using EdgeR.

Results: At early time points (12–36 hour), both control and Tr14-treated wounds showed marked increase in the inducible COX2 enzyme mRNA, while diclofenac-treated wounds did not, likely due to blocking the PGE2 necessary for the feed-back induction. Tr14, in contrast, had a striking inhibitory effect on mRNA levels