Oxylipin networks differ across disease stages during the very early phase of RA, and can inform on specific signatures related to the disease progression. Oxylipins can delineate profiles with clinical relevance and are able to predict treatment response.

**Figure:**

**THU0065**

Oxylipin Profiling during the Very Early Phase of Rheumatoid Arthritis: Associations with Disease Stage, Clinical Features and Treatment Response

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**Background:** traditional approaches and lipomics support the relevance of eicosanoids in rheumatic conditions, such as rheumatoid arthritis (RA). Previous studies from our group and others have revealed altered levels of arachidonic acid in RA, pointing to a possible consumption or enhanced metabolism. However, the potential alterations of its actual metabolites are difficult to assess with conventional approaches, and new, targeted, high-throughput technologies are needed. More importantly, whether these alterations are related to the disease course and could be found at the very early stage of the disease is unknown.

**Objectives:** to characterize the eicosanoid profiles during the earliest stages of RA and their potential clinical associations.

**Methods:** 60 very early RA patients (50 recruited at diagnosis and treatment-naïve) fulfilling 2010 ACR/EULAR criteria, 11 clinical suspect arthralgia (CSA) individuals and 28 healthy controls (HC) were recruited. Samples were collected at the moment of the diagnosis. Serum oxylipins profiles were analyzed by mass spectrometry (LC-MS/MS). Treatment-naïve patients underwent conventional DMARD treatment and were followed for 6 (n=49) and 12 months (n=38). Data analysis was performed in R and MetaboAnalyst.

**Results:** A total of 75 oxylipins, mostly derived from arachidonic (AA), eicosapentaenoic (EPA) and linoleic (LA) acid, were identified. No effect was observed for age, gender or BMI. Correlation and network analyses revealed different patterns among oxylipins across RA patients, CSA and HC (Figure 1A). The 8-HETE, PGE3 and 20-HETE showed the pattern (linear increase) HC→CSA→RA (p=1.47×10^{-4}, 5.34×10^{-4} and 5.68×10^{-4}, respectively; and adjusted FDR=0.050) (Figure 1B). A PLS-DA (explaining 12.3% of the total variance, with a 71.0% cross-validation accuracy and permutation p=5.10^{-4}) confirmed that oxylipins profiles differ among groups, although a certain overlap existed. A total of 22 oxylipins had VIP scores>1 (Figure 1C), which allowed confirming the identification of two clusters (I and II). Cluster usage (I/II) differed among groups (p=0.003): HC (27/1), CSA (7/4) and RA (37/23). Patients exhibiting disease activity showed higher VAS global assessment (p=0.016) and pain (p=0.003) than their cluster I-counterparts. More importantly, cluster II patients were less likely to achieve DAS28 remission at 6 (12/17 vs 10/32, p=0.008) and 12 months (6/9 vs 9/29, p=0.066) upon conventional DMARD treatment compared to those showing cluster I.

OPLS-DA analyses revealed a good discrimination between CSA and HC groups, and 7 compounds (13-HODE, PGDB, 9-oxo-ODE, 12-oxo-EET, 19,20-di-HDPA, 5-HETE and 15-HEPE) were associated with the course HC→CSA. Different precursors (2 LA, 3 AAA, 1 EPA and 1 DHA) and pathways were noted (3 LOX, 4 CYP450). Regarding RA subsets, differences were noted by seropositivity. Whereas 9 compounds were associated with the pattern HC→seronegative RA (8-HETE, PGE3, 20-HETE, 19,20-di-HDPA, PGEM, PGJ2, 12-oxo-LTB4, 14,15-EET and LTB4), a distinct set was observed for the pattern HC→seropositive RA (20-ch-PE, PGE3, 12-oxo-ETE, 20-HETE, PGE3, 4-HDHE, LTB4, 9-oxo-OE, 12-oxo-LTB4, 8,9-EET). No differences in the major pathways were noted.

**Conclusion:** Oxylipin networks differ across disease stages during the very early phase of RA, and can inform on specific signatures related to the disease progression. Oxylipins can delineate profiles with clinical relevance and are able to predict treatment response.

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