DOCTORAL THESIS SUMMARY

Transcriptome assessment and integration with genetics to understand inflammation in gout and hyperuricemia

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THESIS TABLE OF CONTENTS

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PUBLICATION LIST

1. Nica V, Gaal O, Badii M, Cabău G, Mirea AM, Hotea I, Pamfil C, Rednic S, Popp RA, Netea MG, Crișan TO, Joosten LAB, Hint Consortium. Gout Risk Allele Regulating *IRF5* Expression Is Associated with Enhanced IL-1β Production in Response to Palmitate and Monosodium Urate Crystals. Int J Mol Sci. 2025 Oct 12;26(20):9930. doi: 10.3390/ijms26209930. PMID: 41155224; PMCID: PMC12563284.
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INTRODUCTION

Gout is the most common inflammatory arthritis in adults with a raising prevalence world-wide, however the pathophysiology of the underlying inflammatory processes is still not perfectly understood. Elevated serum urate or hyperuricemia is an asymptomatic state required for Monosodium Urate (MSU) deposition and the development of gout. The presence of crystals can be detected in hyperuricemic individuals and is estimated at 20-30%. This implies that MSU crystals cannot induce gout flares alone unless additional factors are involved or specific conditions are met. This was later proven in mice models when sterile MSU crystals failed to induce arthritis.

Soluble urate was also shown to have a pro-inflammatory effect. *In vitro* experiments described downregulation of IL-1Ra production in human monocytes after their pre-treatment with urate by one day followed by stimulation with lipopolysaccharide LPS, a mechanism that involved Akt-Pras40 signaling.

This thesis aims to examine the transcriptomic effects associated with MSU and soluble urate through investigation of Peripheral Blood Mononuclear Cells (PBMC) *in vivo* and *in vitro* experiments. The first study explores the transcriptomic and cytokine response associated with PBMC stimulations with palmitate, LPS with and without MSU crystals as well as MSU crystals alone. The second analysis is the investigation of freshly isolated PBMCs and CD14 monocytes in normouricemic, hyperuricemic individuals and gout patients. The last study evaluates the recently discovered gout risk polymorphism rs4728141. The investigation includes genetic, proteomic, transcriptomic and immunological evaluation to assess how rs4728141 increases the risk to develop gout.

This doctoral research contributed to the creation of an important resource used in multiple research studies that furthered our understanding of the immune responses as well as the role of multiple genetic polymorphisms in gout. The obtained data will continue to provide important information for future research in hyperuricemia, gout and other inflammatory diseases or associated conditions.

The results were disseminated as part of international conferences: “European Crystal Network” and “Gout, Hyperuricemia and Crystal-Associated Disease Network”.

CURRENT STATE OF KNOWLEDGE

Gout can be described as a typical innate immune response induced by MSU crystal deposition. The challenge leads to the release of cytokines and chemokines, that recruit other immune cells to promote and maintain the local inflammation. During a flare, the microscopic examination of the synovium and synovial fluid show significant infiltration with neutrophils, and to a slightly lesser degree with circulating monocytes, macrophages and lymphocytes can also be found. It is currently unknown which cellular component initiates the inflammation, but evidence points towards mononuclear cells. Both monocytes and macrophages can respond to MSU by releasing IL-1β. Synovicites are capable of a similar response as well, however to a significantly lesser degree. Phagocytosis of MSU by neutrophils result in their controlled death through activation of autophagy pathways and formation of neutrophil extracellular traps, which play an important role in the remission phase of the inflammatory response. Lymphocytes generally do not respond to MSU, however still possess a regulatory role in gout by inhibiting the NLRP3 inflammasome.

Urate is a heterocyclic organic compound and the final product of purine metabolism in humans. Despite possessing antioxidant proprieties, which are generally associated with anti-inflammatory effects, extracellular urate was shown many times to be a proinflammatory agent. Urate can promote neutrophil recruitment in liver injury and given that its intracellular concentration is significantly higher, cellular death would result in increased local urate concentration, potentially classifying it as a Damage Associated Mollecular Pattern. Further investigation into the pro-inflammatory proprieties of soluble urate identified a priming effect on monocytes. Pre-treatment with high concentrations of urate followed by a stimulation with TLR agonists resulted in higher IL-1β production paired with a reduction in IL-1RA. 9 This effect was dependent on phosphorylation of Protein kinase B (AKT) and proline-rich AKT substrate 40 kDa (PRAS40) and activation of the mTOR pathway, which inhibits autophagy.

PERSONAL CONTRIBUTIONS

Study 1: MSU crystals exposure is associated with limited transcriptional changes in primary human PBMCs

Objectives: 1) To examine the IL-1β response to MSU crystals alone or in combination with palmitate in multiple larger cohorts to confirm or infirm the previously reported findings; 2) assess the transcriptomic signature in PBMCs after 24-hour stimulation with palmitate, LPS with and without MSU crystals.

Materials and methods: PBMCs were isolated by density gradient centrifugation and were stimulated for 24 hours with palmitate in the presence or absence of MSU crystals,

followed by cytokine production measurement by ELISA. Two bulk RNA-sequencing analyses were performed independently following the same experimental conditions using PBMCs of patients with gout stimulated with medium control, palmitate and LPS in the presence or absence of MSU crystals.

Results: MSU crystals alone induced a small but significant increase in IL-1β production in human PBMCs. IL-1β production was significantly increased when PBMCs were stimulated with palmitate and this was further amplified by the palmitate-MSU combination. Of high interest, MSU crystals alone or in combination with other stimuli caused no significant transcriptomic alterations.

Conclusions: We confirm the synergistic effect of MSU crystals with palmitate that leads to higher IL-1β production. Transcriptomic analysis shows that MSU crystal exposure is not associated with major transcriptional changes in PBMCs. This suggests that the production of IL-1β in response to MSU crystals may largely be regulated at the post-transcriptional level and additional synegistic stimuli are likely required to fully explain the inflammatory response observed clinically in gout. Moreover, this could also bear relevance for other metabolic disorders associated to hyperuricemia where asymptomatic MSU crystal deposition may be present.

Study 2: Transcriptomic Analysis links the changes in hyperuricemia to neutrophilia and identifies key inflammatory pathways in gout

Objectives: To explore the PBMC transcriptomic signatures in hyperuricemia and gout in order to identify new pathways for future therapeutic strategies.

Materials and methods: Bulk RNA-sequencing from freshly isolated PBMCs was performed in 105 normouricemic controls, 21 hyperuricemic subjects and 71 gout patients. In a subset of 20 controls and 10 gout patients, CD14 + monocytes were isolated to perform another analysis. The identified targets were validated using targeted proteomics assay and specific ELISA.

Results: We initially identify a similar transcriptomic signature in hyperuricemia and gout, that can be grouped into 2 main clusters - neutrophil degranulation and hemoglobin metabolism. The findings were validated by confirming increased protein levels of CXCL1, CXCL9, OSM, LIF, TNFSF11 and soluble IL1R2 in hyperuricemic subjects and gout patients. Adding neutrophil count and hemoglobin level as covariates identifies additional changes in gout such as upregulation of the JAK/STAT, Circadian Rhythm pathways and NR4A receptors.

Conclusions: The transcriptomic changes in both hyperuricemia and gout are strongly linked to anemia and granulopoiesis, most likely due to increased fraction of low-density neutrophils in PBMCs. This explains most of the changes in hyperuricemia, while gout is associated with a systemic pro-inflammatory signature.

Study 3: Gout risk allele regulating IRF5 expression is associated with enhanced IL-1β production in response to palmitate and monosodium urate crystals

Objectives: To examine the association between rs4728141 and cytokine production in response to various Toll-Like Receptor ligands and describe the transcriptomic and proteomic changes observed in patients with gout and controls in relation to this polymorphism.

Materials and Methods: We examine the transcriptome of freshly isolated PBMCs from 93 healthy donors and 63 gout patients as well as serum inflammatory proteome in 197 control and 195 gout samples. 24-hour stimulation experiments of freshly isolated human PBMCs were performed, followed by RNA-sequencing in 34-41 gout patient samples and cytokine production measurement by ELISA in 135-153 healthy donors and 93-110 gout patients.

Results: The rs4728141 C allele was associated with increased IL-1β expression in unstimulated PBMCs of controls, but not in gout. No association between the polymorphism and serum inflammatory proteome was found. As expected, an increased IRF5 expression was observed in stimulated PBMCs of rs4728141 C allele carriers in response to several stimulations. Interestingly, IL-1β production was specifically enhanced in association to the rs4728141 C allele when cells were stimulated with palmitate with or without monosodium urate crystals.

Conclusions: The recently identified gout risk allele C rs4728141, which maps to the vicinity to the IRF5 gene is associated with elevated proinflammatory responses and this was specifically observed in response to gout-relevant stimulations such as palmitate in presence or absence of monosodium urate crystals. This pattern of cytokine production shows a functional impact of rs4728141 in gout through altered IL-1β production, a main driver of inflammation in gout.

GENERAL CONCLUSIONS

This doctoral research has significantly contributed to the body of research regarding the mechanisms underlying MSU and urate-induced inflammation. It provides a detailed analysis of the transcriptomic signatures and explores genetic, proteomic, and immunological data to provide a comprehensive analysis of the changes associated with hyperuricemia and gout. The thesis presents the following key findings:

- MSU crystals failed to induce significant transcriptomic changes in circulating PBMCs on their own nor in combination with palmitate or LPS.
- Priming monocytes with high concentrations of urate leads to the downregulation of the interferon pathway.
- The transcriptomic changes associated with hyperuricemia in circulating PBMCs can be explained by neutrophilia and anemia.
- Gout is additionally associated with important changes in PBMC transcriptome, affecting circadian rhythm, the JAK/STAT signaling pathway, and cytokine receptor interactions.
- The gout risk allele rs4728141 increases the production of IL-1β induced by palmitate. We propose this as a mechanism that contributes to gout development.

This work explores multiple mechanisms involved in hyperuricemia and gout with results that have important implications, not only for the examined conditions, but potentially all inflammatory diseases and the associated conditions. It explores processess involved in innate immunity and chronic inflammation, which is a requirement for future development of new therapeutic targets and prophylactic measures. Additionally, the data that was generated during this doctoral research represents a valuable resource that will be used for future projects and studies.

NOVELTY AND INNOVATION PRESENTED IN THE DOCTORAL RESEARCH

The thesis offers several important findings for the field of immunology and more specifically advances the understanding of asymptomatic hyperuricemia and gout and the underlying inflammatory processes in both conditions.

The presented research examines how PBMC and monocytes interact with soluble urate and MSU crystals both in vitro and in vivo, providing a holistic view on the processess that control these interactions.

The first study examines the transcriptomic signature in PBMCs after their stimulation MSU crystals, palmitate or a combination of both. These are novel findings that provide additional information in a controversial debate regarding the mechanism through which MSU triggers inflammation. By providing the presented evidence, we argue that MSU does not induce any major transcriptional changes in PBMCs or circulating monocytes and its mechanism of action in these cell types is post-transcriptional.

The transcriptomic responses observed in vivo were significantly different from the experiments performed in vitro. In the third chapter we are able to identify key variables that influence the PBMC transcriptome in hyperuricemia. Furthermore, we identify important pathways that are tied to chronic inflammation, some of which were not previously described in gout.

Lastly, this work examines a recently identified polymorphism associated with gout risk. For that purpose, several omics dataset were investigated and stimulation experiments were performed. We additionally propose a mechanism that explains this association.

REZUMAT AL TEZEI DE DOCTORAT

Evaluarea transcriptomului si integrarea informatiei genetice pentru a intelege inflamatia in guta si hiperuricemie

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CUPRINSUL TEZEI

Cuvinte cheie: Transcriptom, Guta, Hiperuricemie, Inflamatie

LISTA DE PUBLICAŢII

1. Nica V, Gaal O, Badii M, Cabău G, Mirea AM, Hotea I, Pamfil C, Rednic S, Popp RA, Netea MG, Crişan TO, Joosten LAB, Hint Consortium. Gout Risk Allele Regulating *IRF5* Expression Is Associated with Enhanced IL-1β Production in Response to Palmitate and Monosodium Urate Crystals. Int J Mol Sci. 2025 Oct 12;26(20):9930. doi: 10.3390/ijms26209930. PMID: 41155224; PMCID: PMC12563284.
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INTRODUCERE

Guta reprezintă cea mai frecventă artrita inflamatorie la adulti, cu o prevalenta aflata in crestere la nivel mondial, insa fiziopatologia proceselor inflamatorii subiacente inca nu este pe deplin înţeleasa. Nivelurile crescute de urat seric sau hiperuricemia constituie o stare asimptomatică necesară pentru depunerea uratului monosodic (MSU) si dezvoltarea gutei. Prezenţa cristalelor este detectabilă la circa 20–30% dintre indivizii cu hiperuricemie. Acest fapt sugerează ca cristalele nu pot induce singure atacuri de gută decat daca intervin factori suplimentari sau sunt indeplinite anumite conditii specifice. Această ipoteza a fost ulterior confirmată pe modele murine, unde cristalele sterile de MSU nu au indus artrita.

Acidul uric solubil de asemenea exercita un efect proinflamator. Experimentele *in vitro* au descris reducerea productiei de IL-1Ra in monocitele umane după pre-tratarea acestora cu acid uric timp de o zi, urmata de stimularea cu lipopolizaharid (LPS), mecanism ce a implicat semnalizarea Akt-Pras40.

Această teza isi propune sa examineze semnaturile transcriptomice asociate cu MSU si cu acidul uric solubil prin investigarea celulelor mononucleare din sangele periferic (PBMC) atat *in vivo* şi experimental, *in vitro*. Primul studiu prezentat exploreaza raspunsul transcriptomic si citokinic asociat cu stimularea PBMC cu palmitat, LPS cu si fara cristale de MSU, precum si cu cristale de MSU izolate. A doua analiza investigheaza PBMC proaspat izolate si monocitele CD14 la indivizi normouricemici, hiperuricemici si pacienti cu guta. Ultimul studiu evalueaza polimorfismul genetic recent identificat, rs4728141, asociat cu riscul de guta. Investigatia include evaluari genetice, proteomice, transcriptomice si imunologice pentru a determina modul în care rs4728141 creste riscul de dezvoltare a gutei.

Cercetare doctorala a contribuit la crearea unei resurse importante utilizate în multiple studii, care au explorat raspunsurile imune asociate cu hiperuricemia si guta, precum si rolul diferitelor polimorfisme genetice. Datele obtinute vor continua sa ofere informatii esentiale pentru cercetari viitoare asupra bolilor studiate si altor boli inflamatorii sau comorbiditati asociate.

Rezultatele au fost diseminate în cadrul unor conferinte internationale: “European Crystal Network” si “Gout, Hyperuricemia and Crystal-Associated Disease Network”.

STADIUL ACTUAL AL CUNOAȘTERII

Guta poate fi descrisa ca un raspuns imun innascut tipic, indus de depunerea cristalelor de MSU. Aceasta provocare conduce la eliberarea de citokine si chemokine, care recruteaza alte celule imune pentru a promova si mentine inflamatia locala. In timpul unui atac de guta, examinarea microscopica a sinoviului si a lichidului sinovial evidentiaza o infiltrare semnificativa cu neutrofile, dar intr-o masura mai redusa pot fi identificate si monocite circulante, macrofage si limfocite. In prezent, nu este cunoscut care componenta celulara initiaza inflamatia, insa dovezile indica spre celulele mononucleare. Atat monocitele, cat si macrofagele pot raspunde la MSU prin eliberarea de IL-1β. Sinoviocitele sunt, de asemenea, capabile de un raspuns similar, însă cu o intensitate considerabil mai mica. Fagocitoza MSU de catre neutrofile determina moartea controlata a acestora prin activarea cailor de autofagie si formarea de „capcane" extracelulare de neutrofile, care joaca un rol important in faza de remisiune a raspunsului inflamator. Limfocitele, in general, nu raspund la MSU, însa poseda un rol regulator în guta prin inhibarea inflamazomului NLRP3.

Acidul uric este un compus organic heterociclic si produsul final al metabolismului purinelor la om. In ciuda proprietatilor antioxidante, asociate in mod obisnuit cu efecte antiinflamatorii, s-a demonstrat in repetate randuri ca uratul extracelular actioneaza ca agent proinflamator. Uratul poate promova recrutarea neutrofilelor in leziuni hepatice si, avand in vedere ca concentratia sa intracelulara este semnificativ mai ridicata, moartea celulara ar duce la cresterea concentratiei locale de acid uric, putandu-l astfel clasifica drept un semnal molecular asociat cu lezarea (DAMP – Damage Associated Molecular Pattern). Investigatii suplimentare asupra proprietatilor proinflamatorii ale uratului solubil au identificat un efect de priming asupra monocitelor. Pre-tratarea cu concentratii ridicate de urat, urmata de stimularea cu agonisti TLR, a condus la o productie crescuta de IL-1β, asociata cu reducerea IL-1Ra. Acest efect a depins de fosforilarea proteinkinazei B (AKT) si a substratului AKT bogat in prolina de 40 kDa (PRAS40), precum si de activarea caii mTOR, care inhiba autofagia.

CONTRIBUȚII PERSONALE

Studiul 1: Expunerea la cristale de MSU este asociata cu modificari transcriptomice limitate in PBMC umane primare

Obiective: 1) Investigarea raspunsului IL-1β la cristalele de MSU, administrate singure sau in combinatie cu palmitat, in cohorte extinse, pentru a confirma sau infirma rezultatele raportate anterior; 2) Evaluarea semnaturii transcriptomice in PBMC dupa 24 de ore de stimulare cu palmitat, LPS cu si fara cristale de MSU.
Materiale si metode: PBMC au fost izolate prin centrifugare in gradient de densitate si stimulate timp de 24 de ore cu palmitat, in prezenta sau absenta cristalelor de MSU, urmat de masurarea productiei de citokine prin ELISA. Doua analize independente de secventiere ARN in masa au fost realizate, respectand aceleasi conditii experimentale, utilizand PBMC de la pacienti cu guta stimulati cu mediu control, palmitat si LPS, in prezenta sau absenta cristalelor de MSU.

Rezultate: Cristalele de MSU singure au indus o crestere redusa, dar semnificativa, a productiei de IL-1β in PBMC umane. Stimularea cu palmitat a dus la o crestere semnificativa a productiei de IL-1β, care a fost amplificata suplimentar prin combinatia palmitat–MSU. De interes major, cristalele de MSU singure sau in combinatie cu alti stimuli nu au determinat modificari transcriptomice relevante.

Concluzii: Se confirma efectul sinergic al cristalelor de MSU cu palmitatul, care conduce la o productie crescuta de IL-1β. Analiza transcriptomica arata ca expunerea la cristale de MSU nu este asociata cu modificari majore la nivelul transcriptiei in PBMC. Aceasta sugereaza ca productia de IL-1β ca raspuns la cristalele de MSU este reglata preponderent la nivel post-transcriptional si ca stimuli sinergici suplimentari sunt probabil necesari pentru a explica complet raspunsul inflamator observat clinic in guta. In plus, aceste constatari pot avea relevanta si pentru alte tulburari metabolice asociate hiperuricemiei, unde depunerea asimptomatica de cristale MSU poate fi prezenta.

Studiul 2: Analiza transcriptomica asociaza modificarile din hiperuricemie cu neutrofilia si identifica cai inflamatorii-cheie in guta

Obiective: Explorarea semnaturilor transcriptomice PBMC in hiperuricemie si guta, in vederea identificarii unor noi cai cu potential terapeutic.

Materiale si metode: Secventiere ARN din PBMC proaspat izolate a fost realizata la 105 controale normouricemice, 21 de subiecti hiperuricemici si 71 de pacienti cu guta. Intr-un subgrup de 20 de controale si 10 pacienti cu guta au fost izolate monocite CD14+, pentru analize suplimentare. Tintele identificate au fost validate prin teste proteomice tintite si prin ELISA specifica.

Rezultate: Am identificat initial o semnatura transcriptomica similara in hiperuricemie si guta, care poate fi grupata in doua clustere principale: degranularea neutrofilelor si metabolismul hemoglobinei. Rezultatele au fost validate prin confirmarea nivelurilor

proteice crescute de CXCL1, CXCL9, OSM, LIF, TNFSF11 si IL1R2 solubil la subiectii hiperuricemici si pacientii cu guta. Adaugarea numarului de neutrofile si a nivelului de hemoglobina drept covariabile a evidentiat modificari suplimentare in guta, precum activarea cailor JAK/STAT, Ritm Circadian si receptorii NR4A. **Concluzii:** Modificarile transcriptomice din hiperuricemie si guta sunt strans legate de anemie si granulopoeza, cel mai probabil datorita fractiunii crescute de neutrofile cu densitate scazuta in PBMC. Acestea explica majoritatea modificarilor din hiperuricemie, in timp ce guta este caracterizata printr-o semnatura proinflamatorie sistemica.

Studiul 3: Alela de risc pentru guta care regleaza expresia IRF5 este asociata cu productia crescuta de IL-1β ca raspuns la palmitat si cristale de urat monosodic **Obiective:** Investigarea asocierii dintre rs4728141 si productia de citokine ca raspuns la diversi liganzi Toll-Like Receptor, precum si descrierea modificarilor transcriptomice si proteomice observate la pacienti cu guta si controale in functie de acest polimorfism. **Materiale si metode:** A fost examinat transcriptomul PBMC proaspat izolate de la 93 de donatori sanatosi si 63 de pacienti cu guta, precum si proteomul seric inflamator la 197 de controale si 195 de pacienti cu guta. Au fost realizate experimente de stimulare timp de 24 de ore pe PBMC proaspat izolate, urmate de secventiere ARN la 34–41 pacienti cu guta si de masurarea productiei de citokine prin ELISA la 135–153 donatori sanatosi si 93–110 pacienti cu guta.

Rezultate: Alela C a rs4728141 a fost asociata cu o expresie crescuta a IL-1β in PBMC nestimulate de la controale, dar nu si la pacientii cu guta. Nu s-a constatat nicio asociere intre polimorfism si proteomul inflamator seric. Dupa cum era de asteptat, o expresie crescuta a IRF5 a fost observata in PBMC stimulate ale purtatorilor alelei C, ca raspuns la mai multe tipuri de stimulare. Interesant, productia de IL-1β a fost amplificata specific in asociere cu alela C a rs4728141 atunci cand celulele au fost stimulate cu palmitat, cu sau fara cristale de urat monosodic.

Concluzii: Alela C a rs4728141, recent identificata ca factor de risc pentru guta si localizata in vecinatatea genei IRF5, este asociata cu un raspuns proinflamator crescut, observat in mod particular la stimulari relevante pentru guta, precum palmitatul si cristalele de MSU. Acest tipar de productie a citokinelor indica un impact functional al rs4728141 in guta prin modificarea productiei de IL-1β, principal mediator al inflamatiei in aceasta boala.

CONCLUZII GENERALE

Cercetarea prezentata in aceasta teza doctorala a contribuit semnificativ la intelegerea mecanismelor care stau la baza inflamatiei induse de cristalele de MSU si de urat. Aceasta ofera o analiza detaliata a semnaturilor transcriptomice si exploreaza date genetice, proteomice si imunologice pentru a furniza o evaluare comprehensiva a modificarilor asociate cu hiperuricemia si guta. Teza prezinta urmatoarele concluzii:

- Cristalele de MSU nu au indus modificari transcriptomice semnificative in PBMC, nici singure, nici in combinatie cu palmitat sau LPS.
- Stimularea monocitelor cu concentratii inalte de acid uric solubil duce la inhibarea caii de semnalizare a interferonului de tip 1.
- Modificarile transcriptomice asociate cu hiperuricemia in PBMC pot fi explicate prin neutrofilie si anemie.
- Guta este asociata suplimentar cu modificari importante in transcriptomul celulelor mononuclear din sange, care afecteaza ritmul circadian, calea de semnalizare JAK/STAT si interactiunile receptorilor de citokine.
- Alela de risc pentru guta rs4728141 creste productia de IL-1β indusa de palmitat. Propunem acest mecanism ca o contributie la dezvoltarea gutei.

Aceasta lucrare investigheaza mecanismele implicate in raspunsurile imune din hiperuricemie si guta, cu rezultate care au implicatii importante nu doar pentru conditiile analizate, ci potential pentru toate bolile inflamatorii. Ea contribuie la consolidarea cunostintelor existente in vederea intelegerii imunitatii innascute si a inflamatiei cronice, ceea ce reprezinta o premisa necesara pentru dezvoltarea viitoare a unor noi tinte terapeutice si masuri profilactice. Datele generate in cadrul acestei cercetari doctorale constituie o resursa valoroasa ce va fi utilizata in proiecte si studii viitoare.

ORIGINALITATEA ŞI CONTRIBUŢIILE INOVATIVE ALE CERCETĂRII DOCTORALE

Aceasta teza ofera o serie de observatii importante in domeniul imunologiei si reumatologiei, si mai specific despre hiperuricemia asimptomatica si guta, precum si a proceselor inflamatorii care stau la baza acestor patologii.

Cercetarea prezentata investigheaza modul in care celulelele monucleare sangvine interactioneaza cu acidul uric solubil si cristalele de monosodiu, atat in vitro, cat si in vivo, oferind astfel o perspectiva holistica asupra proceselor care regleaza aceste interactiuni.

Primul studiu examineaza semnatura transcriptomica in celule mononucleare dupa stimularea lor cu cristale de MSU, palmitat sau combinatia acestora. Aceste rezultate reprezinta descoperiri noi, care aduc date suplimentare intr-o dezbatere controversata privind mecanismul prin care MSU declanseaza inflamatia. Pe baza dovezilor prezentate, argumentam ca MSU nu induce modificari transcriptomice majore in PBMC sau monocitele circulante, iar mecanismul sau de actiune preponderent post-transcriptional.

Raspunsurile transcriptomice observate in vivo au fost semnificativ diferite de cele in vitro. In al doilea studiu au fost identificati toti factorii-cheie care influenteaza transcriptomul PBMC in hiperuricemie. Mai mult, au fost evidentiate cai importante legate de inflamatia cronica, care nu au fost descrise anterior in guta.

Studiul final investigheaza un polimorfism recent identificat, asociat cu riscul de guta. In acest scop au fost analizate mai multe seturi de date omice si au fost realizate experimente de stimulare. De asemenea, propunem un mecanism care explica aceasta asociere.