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Moving towards personalized medicine in rheumatoid arthritis: Methotrexate cellular pathways as pharmacogenetic predictors of Methotrexate therapeutic outcome

Aurea Rosa Nunes Pereira Lima

Cooperativa De Ensino Superior Politécnico Universitário, CRL, Portugal

Medicine was always personalized but only in this century the integration of patient genome was considered as an important factor responsible for intra and inter-patient drug therapeutic outcome variability. One of the major contributors for this development is Pharmacogenomics (PGx), which represents the use of individual genetic data to predict therapeutic outcome and tailor the best medical intervention to each patient. During the past decade there has been a considerable research effort towards PGx. But, translating PGx knowledge into clinical practice is still a major challenge, particularly in case of highly complex diseases such as rheumatoid arthritis (RA). RA is a systemic autoimmune disease characterized by chronic inflammation of multiple peripheral joints for which the "gold standard" drug is methotrexate (MTX). Literature suggests that RA patients' genetic profile may have a significant role in therapeutic outcome variability observed among patients, particularly genes encoding proteins involved in RA pathophysiology and those involved in MTX action mechanism. MTX action mechanism include: (1) MTX membrane transport pathways, a network of transporters which allow MTX influx and efflux, that belong to two major superfamilies': Solute carriers (SLCs) and adenosine triphosphate (ATP)-binding cassette (ABCs) transporters and, (2) MTX intracellular pathways, which include polyglutamation, folate, methionine, adenosine and de novo synthesis of purines and pyrimidines pathways. From 49 SNPs in genes encoding for proteins involved in MTX action mechanism studied in 233 RA patients, 14 genotypes could be predictors of MTX non-response, as follow *SLC22A11* rs11231809 T carriers, *ABCC1* rs246240 G carriers, *ABCC1* rs3784864, *TYMS* rs34743033 3R3R, *TYMS* rs34743033+rs2853542 3RC3RG, *TYMS* rs34489327 6bp- carriers, *MTHFR* rs1801131 AA, *MTHFR* rs1801133 TT, *MS* rs1805087 AA, *MTRR* rs1801394 A carriers, ATIC rs2372536 C carriers, ATIC rs4673993 T carriers, ATIC rs7563206 T carriers and ATIC rs12995526 T carriers. In addition, 8 genotypes could be predictors of MTX-related toxicity, as follow *SLC19A1* rs7499 G carriers, *SLC46A1* rs2239907 GG, *SLCO1B1* rs4149056 T carriers, ATIC rs2372536 G carriers, ATIC rs3821353 T carriers, ATIC rs7563206 CC, ATIC rs12995526 CC and *ADORA2A* rs2267076 T. Interestingly, from the 24 studied genes encoding for crucial proteins involved in MTX action mechanism, 12 genes demonstrated to be putative predictors of MTX therapeutic outcome. Therefore, genotyping patients according to these genetic markers may be helpful to identify which patients will not benefit from MTX treatment, highlighting the relevance of developing the field of personalized medicine. Nevertheless, and despite the potential of these findings, translation into clinical practice requires larger and multicentric studies in order to clear endorse the utility of the recently gather results.

Biography

Aurea Rosa Nunes Pereira Lima has completed her Bachelor's degree in Pharmaceutical Sciences in 2004 at CESPU, Master's degree in Medicine and Molecular Oncology in 2007 at Faculty of Medicine, University of Porto (FMUP), Doctorate degree in Medical Sciences in 2014 at Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto and also completed the Integrated Master Course in Medicine at ICBAS. She is currently a Professor and Researcher at Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, CESPU and has 15 papers in scientific journals.

aurea.lima@iucs.cespu.pt

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