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Studying methotrexate therapeutic activity in Chikungunya-related human arthritis

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Methotrexate (MTX), the first line disease modifying anti-rheumatic drug in rheumatoid arthritis (RA) therapy, has been used successfully to treat patients with rheumatoid-like arthritis post-Chikungunya virus (CHIKV) infection (1). However, mechanisms by which MTX exerts its therapeutic effect are poorly understood. The eicosanoid prostaglandin (PG) E2 is one of the most important mediators of inflammation and contributes to several pathogenic features of arthritis such as pain and bone destruction (2,3). The proinflammatory cytokines IL-1β and TNFα, which play a pivotal role in initiating and driving RA, are known to enhance PGE2 production (4). We herein used a model of primary human synovial fibroblasts (HSF) infected with CHIKV or stimulated by the synthetic molecule polyriboinosinic:polyribocytidylic acid (PIC) to mimic chronic viral infection (5) and assessed the potential pharmacological effects of MTX. By quantitative RT-PCR, we found that PIC but not CHIKV increased the mRNA level of group IVA cytosolic phospholipase A2 (cPLA2α) (6) , a central enzyme in AA-derived eicosanoid production. Similarly, PIC but not CHIKV upregulated mRNA expression of the microsomal prostaglandin E2 synthase 1 (mPGES-1) (7) enzyme involved in PGE2 synthesis. In contrast, we found that PIC and CHIKV enhanced mRNA expression of cyclooxygenase 2 (COX-2) (4) , a major PGE2 biosynthetic enzyme. Moreover, PIC and CHIKV decreased mRNA expression of the PGE2 degrading enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH) (8) and this effect was not modulated by MTX. As controls, we found that IL-1β as well as TNFα stimulated mRNA levels of PLA2, COX-2, mPGES-1 and all these effects were inhibited by dexamethasone (DXM). DXM, in contrast, upregulated mRNA expression of the PGE2 degrading enzyme (15-PGDH). These original data argue for a therapeutic activity of MTX independently of PGE2 regulated response and through novel mechanisms which remain to be explored.

Recent Publications:

1. Javelle E, Ribera A, Degasne I, Gaüzère B-A, Marimoutou C, Simon F. Specific Management of Post-Chikungunya Rheumatic Disorders: A Retrospective Study of 159 Cases in Reunion Island from 2006-2012. PLoS Negl Trop Dis. 2015.
2. Fattahi MJ, Mirshafiey A. Prostaglandins and Rheumatoid Arthritis. Arthritis. 2012.
3. Hoxha M. A systematic review on the role of eicosanoid pathways in rheumatoid arthritis. Adv Med Sci. 2018 Mar 1;63(1):22–9.
4. Martel-Pelletier J, Pelletier J-P, Fahmi H. Cyclooxygenase-2 and prostaglandins in articular tissues. Semin Arthritis Rheum. 2003 Dec 1;33(3):155–67.
5. Bedoui Y, Giry C, Jaffar-Bandjee M-C, Selambarom J, Guiraud P, Gasque P. Immunomodulatory drug methotrexate used to treat patients with chronic inflammatory rheumatisms post-chikungunya does not impair the synovial antiviral and bone repair responses. PLoS Negl Trop Dis. 2018 Aug 3;12(8):e0006634.
6. Sommerfelt RM, Feuerherm AJ, Jones K, Johansen B. Cytosolic Phospholipase A2 Regulates TNF-Induced Production of Joint Destructive Effectors in Synoviocytes. PLOS ONE. 2013 Dec 12;8(12):e83555.
7. Kojima F, Matnani RG, Kawai S, Ushikubi F, Crofford LJ. Potential roles of microsomal prostaglandin E synthase-1 in rheumatoid arthritis. Inflamm Regen. 2011 Mar;31(2):157–66.
8. Tai H-H, Ensor CM, Tong M, Zhou H, Yan F. Prostaglandin catabolizing enzymes. Prostaglandins Other Lipid Mediat. 2002 Aug 1;68–69:483–93.

Biography

Yosra Bedoui obtained her degree of doctor of pharmacy in 2014 at Monastir University, Tunisia. She is currently in her third year of her PhD at the University of La Reunion, France. She is working at the UMR PIMIT. Her thesis is devoted to the evaluation of the immunomodulatory and anti-viral role of methotrexate in the context of chronic arthritis induced by Chikungunya virus infection. Her interests are focused on the study of the physiopathological mechanisms of chronic arthritis induced by Chikungunya virus and the immunomodulatory effects of methotrexate treatment.

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