Characterization of Monocytes and Macrophages in Rheumatoid Arthritis Patients: their role in the therapy response.

D. Sola[1,2], A. Amoruso[1], G.L. Camaschella[1], D. Michelone[1], L. Rossi[2], P.P. Sainaghi[1], M. Pirisi[2], S. Brunelleschi[1]

[1]Dept. of Health Sciences, University 'A. Avogadro', Novara (Italy); [2]Internal Medicine 1, Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara (Italy).

Rheumatoid Arthritis (RA) is a systemic autoimmune disease with unknown aetiology, characterized by a symmetrical erosive synovitis [1]. If not properly treated the course of the disease can be very severe, leading to deformity and permanent disability. A significant improvement of survival and quality of life is obtainable with an appropriate and early treatment [2]. Currently many drugs are available, but they can be very expensive, not always effective, and also not adverse effect free. Therefore it is crucial to identify any predictor marker to choose best therapy for each patient. It is known that monocytes play a central role in the development and progress of RA since they are involved in antigen recognition, activation of osteoclasts and production of inflammatory cytokines, reactive oxygen species (ROS) and metalloproteinases (MMP) [3]. Peroxisome Proliferator-Activated Receptor (PPAR)γ is expressed by major cell populations in the joints [4] and its agonists exert anti-inflammatory effects in experimental RA [5]. In this regard, we have published a pilot study demonstrating that RA patients had significantly enhanced PPARγ expression and MMP-9 activity, as compared to healthy donors. Interestingly, cells from patients with less active disease (DAS-28<3.2) present higher PPARγ expression and lower MMP-9 activity than RA patients with DAS-28<3.2 [6]. Recently, it has emerged the involvement of the microparticles (MPs) in rheumatoid disease [7]. MPs are small membrane-bound particles originating from different cell types during activation or apoptosis: they mediate intercellular communications, exert pro-coagulant activity (especially if phosphatidylserine positive MPs) and affect inflammation and several patho-physiological conditions [8-10]. Therefore, it will be interest to investigate the responsiveness of monocytes and monocyte-derived MPs in the disease progression and in therapy response. Monocytes were isolated from heparinised venous blood of patients with RA (according to ACR and EULAR criteria) [11-12] and from healthy volunteers (as control) and differentiated to macrophages. Superoxide anion (O2-) production and PPARγ expression were evaluated as functional cell parameters. MPs were collected from platelet-poor plasma and from monocytes and immediately used for FACS evaluation. Preliminary results shown a significant inverse correlation between the $CD14^+/CD206^+$ cell subpopulation and the indices of disease activity (DAS28, CDAI, SDAI) ($n=26$, $p<0.05$); moreover, CD206 expression on monocytes/M2 macrophages of patients was 2 fold increased than in controls. These data positively correlated with the increased content of Annexin V positive MPs in PP-plasma, leading us to hypothesize a possible cross-talk between MPs and macrophage polarization. The basal ROS production in patients was higher than in the healthy donors, and the PGJ2 attenuated the PMA (the gold standard for cell activation) effect in patient cells probably attending in PPARγ signalling pathway activated by the therapy. Moreover, we challenged healthy donor monocyte/macrophages with several RA-therapy drugs to evaluate their possible involvement in cell activation. Results demonstrated that Leflunomide, MTX and Etanercept significantly decreased the PMA-ROS production confirming a direct effect of the therapy on the monocyte responsiveness.

1. Harris ED (1990) N Eng J Med; 322: 1277-1289
2. Gabriel SE et al (2003) Arthritis Rheum; 48: 54-58
3. Gravallese EM et al (2000) Arthritis Rheum; 43: 250-8
4. Giaginis et al. (2009) Pharmacol Res. 60:160-9
5. Cuzzocrea et al. (2003) Arthritis Rheum. 48:3544-56
6. Palma A et al, (2012) Rheumathology 51:1942-52
7. Prati C et al (2010) Joint Bone Spine;77:496-8
8. Nomura S et al (2008) Thromb Res; 123: 8-23
9. Anderson HC et al (2010) Lab Invest; 90:1549-1557
10. Hugel B et al (2005) Physiology; 20: 22-27
11. Aletaha D et al (2010) Ann. Rheum. Dis;69: 1580–8
12. Arnett F et al (1988) Arthritis Rheum 31: 315–24