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Targeting IL-10, ZO-1 gene expression and IL-6/STAT-3 trans-signaling by a combination of atorvastatin and mesalazine to enhance anti-inflammatory effects and attenuate progression of oxazolone induced colitis

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Ulcerative colitis (UC), one of the two main inflammatory bowel diseases (IBD) together with Crohn's disease, is a chronic, relapsing disease of the colon (although extra-intestinal manifestations are not uncommon [1] with an increasing incidence in developing countries [2]. Understanding its ~~aetiology~~ **aetiology** is of paramount importance to find a curative treatment. Genetic, immune system, gut permeability, microbiome, and environment (diet) are the main actors [3].

More than 250 genes are involved in **the** pathogenesis of IBD: such a high number means that none of these genes are of paramount importance alone. One key aspect that ~~is in common among all of~~ all these genes **have in common** is that they codify for proteins involved in the recognition of bacteria in the gut microbiome [4]. A ~~disregulate~~ **deregulated** immune system, with a deficit in innate response (deficit in defensins), with a consequent overactivation of the adaptative response (lymphocyte T cell-mediated) is the key factor of inflammation onset and persistence [4]. A billion of antigens pass through the intestinal lumen every day. Gut permeability is a modulable feature of the intestinal epithelium, finely regulated by several proteins, of which zonulin is **was** the most studied over the past two decades [5]. Zonulin is a 47-kDa protein that increases intestinal barrier permeability through the rearrangement of actin microfilaments that leads to the displacement of tight junction proteins [6].

The aim of the current treatment regimen in UC is to treat relapses and maintain remission, with as few side effects as possible [7]. Mesalazine is the cornerstone of the treatment of UC; however, this drug is able to induce and maintain remission in about 50-60% of patients **only** [8]. Therefore, there is an urgent need for new treatment options to improve the long-term control of the disease.

Atorvastatin is a member of the drug class known as statins. Statins are widely used to reduce cholesterol levels by inhibiting hydroxymethylglutaryl-coenzyme A reductase, and to improve the natural history of patients at risk of cardiovascular events [9]. Statins are not currently part of the standard treatment of UC in international guidelines, and conflicting results have been reported

concerning the effect of statins in patients affected by UC [10,11].

In the study of El-Mahdy et al., the authors analysed the effect of atorvastatin, added to mesalazine, in controlling the inflammation in a rat model of oxazolone-induced ulcerative colitis [12]. They found that treatment with atorvastatin (20 mg/kg/day) in combination to mesalazine was more effective compared to no treatment and to treatment with either mesalazine or atorvastatin alone. Rats treated with combination therapy showed an increase in colon length, a decrease in colon wet mass index, an increase in body weight, and an improvement of diarrhoea and rectal bleeding. Furthermore, combination therapy was able to restore intestinal permeability inducing an increased expression of tight junction protein ZO-1 (zonula occludens). Concurrently, the authors observed an overall improvement of the inflammatory status; the expression of the anti-inflammatory interleukin-10 (IL-10) significantly increased [12], while the expression of pro-inflammatory factors, such as IL-6, distinctly decreased [13].

However, these results should be interpreted with caution. Firstly, a dosage of 20 mg/kg/day is not applicable in humans where 10-80 mg/die is the therapeutic range. Secondly, the rat model of inflammation is characterized by a T-helper 2-mediated colitis, limited to the distal half of the colon. Finally, available clinical studies reported contradictory results on the efficacy of statins administration in patients with UC, as mentioned above.

In the next future, double-blind randomized controlled trials including large cohorts of patients affected by UC are warranted to evaluate and corroborate these preliminary results in the clinical setting. In particular, the appropriate dose [13], and treatment duration are two of the main questions that remain to be solved in the next studies.

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