**Fpr2/ALX is a Potential Therapeutic Target for the Treatment of Sepsis**

Ellen Hughes¹, Julia Buckingham², Felicity Gavins¹

¹Wolfson Neuroscience Laboratories, Imperial College London, London W12 0NN, United Kingdom,
²Division of Diabetes, Endocrinology and Metabolism, Imperial College London, London W12 0NN, United Kingdom

Sepsis is a state of acute systemic inflammation that can occur following bacterial infection. Annual death rates are around 1.8 million people worldwide, due in part to inefficacy of existing drugs. Formyl peptide receptor 2 (Fpr2/ALX) is a receptor highly expressed in leukocytes, and has been shown to be involved in the resolution of inflammation. The role of this receptor in sepsis is currently unknown and so we chose to investigate it using a murine model of experimental endotoxaemia.

C57BL/6 mice were treated with lipopolysaccharide (LPS; 10μg/mouse i.p.; n=5 mice/group) for 2h, with a drug injection into the tail vein after 20 min. After 2h, mice were anaesthetised with ketamine (150mgkg⁻¹) and xylazine (7.5mgkg⁻¹) and the inflammatory response was quantified in vivo in terms of leukocyte-endothelium interactions in mesenteric venules, using the specialised technique of intravital microscopy. Administration of Fpr2/ALX agonists, Ac2-26 (100μg/mouse) and LXA₄ (0.11μg/mouse), significantly reduced LPS-induced leukocyte adherence versus vehicle-treated animals (7.3 ± 0.9 cells with vehicle, and 2.9 ± 0.3 cells with Ac2-26 and 3.3 ± 0.3 cells with LXA₄; p<0.05 vs. LPS + vehicle). The anti-adhesive effect of both ligands was blocked by co-administration of the pan-Fpr antagonist Boc2 (10μg/mouse), to 8.2 ± 0.9 cells with Ac2-26 + Boc2 and 6.1 ± 0.6 cells with LXA₄ + Boc2 (p>0.05 vs. agonist alone and p>0.05 vs. LPS + vehicle). Although leukocyte emigration and plasma leakage were increased above baseline values by LPS administration, and leukocyte rolling velocity was decreased, no significant effect of any drug treatment was observed.

A real-time detachment protocol confirmed the anti-adhesive properties of both Fpr2/ALX agonists and showed that effects are rapidly manifested. After 2h LPS treatment, Ac2-26 or LXA₄ were administered via the jugular vein and the number of adherent leukocytes in mesenteric venules was measured (n=5 mice/group). Both agonists caused significant detachment of adherent leukocytes compared to vehicle within 10 min of administration, with only 43.2 ± 8.8% cells still adherent with Ac2-26 treatment and 55.6 ± 2.3% with LXA₄. Interestingly, the degree of detachment caused by LXA₄ at 10 min was significantly less than with Ac2-26 (a difference of 12.4%; p<0.05), but by 15 min LXA₄ treatment the degree of detachment had reached similar levels (41 ± 4.4%).

To conclude, these novel data indicate that agonists for Fpr2/ALX can reduce inflammation caused by LPS, suggesting a potential therapeutic target for treating sepsis.