Oxidative Stress in Endometriosis Induces IL-8 Release Directly via 4-HNE.

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INTRODUCTION: Lipid peroxidation products, e.g. 4-hydroxynonenal (4-HNE), are generated by oxidative stress, and are suggested to cause endometriosis-associated pain following iron overload after retrograde menstrual bleeding. Our aim was to determine the role of oxidative stress including 4-HNE protein adduct formation in endometriotic lesions and in peritoneal fluid from endometriosis patients; and characterise the proinflammatory effects caused by 4-HNE in endometriosis.

METHODS: Peritoneal fluid, eutopic endometrium/ectopic lesions from women with endometriosis (n=41) and controls (n=18) collected according to WERF EPHect criteria were used in proteomic analysis, Western blotting and immunohistochemistry. Cytokine levels in peritoneal fluid samples of cases (n=69) and non-endometriotic controls (n=29) and in supernatants from 4-HNE-treated THP-1 monocytic cells and human peripheral blood mononuclear cells (PBMC) were measured using the V-PLEX Human Cytokine 36-Plex Kit.

RESULTS: Ectopic lesions were characterized by widespread 4-HNE modifications and infiltration of CD68+ and CD163+ macrophages. Significantly higher ($p < 0.001$) levels of oxidative modification of aspartic acid, phenylalanine, lysine, asparagine, proline, arginine and tyrosine amino acid residues were observed in ectopic vs. eutopic samples from cases. IL-8 was significantly elevated in peritoneal fluid of cases vs. controls, and was secreted from THP-1 and PBMC in a 4-HNE concentration-dependent manner.

CONCLUSION: Peritoneal fluid and ectopic lesions from women with endometriosis showed pronounced signs of oxidative stress e.g. posttranslational protein modifications, 4-HNE adducts, as well as infiltration of CD68+ and CD163+ macrophages. The observed effects of 4-HNEinduced IL-8 release from monocytes indicates a further mechanism by which elevated IL-8 levels can promote immune cell infiltration and angiogenesis in lesions.