

## **Role of omega-3-derived lipid mediators in the resolution of inflammation in insulin-sensitive tissues.**

Joan Clària

Biochemistry and Molecular Genetics Service-Hospital Clínic and Department of Biomedicine-School of Medicine-University of Barcelona, Barcelona, Spain.

Omega-3-polyunsaturated fatty acids exert well-documented protective effects. The beneficial actions of omega-3 fatty acids, especially as anti-inflammatory and immunoregulatory compounds, are attributed not only to the inhibition of inflammatory factors but also to the conversion of these essential fatty acids into a novel class of biologically active lipid mediators. This novel family of omega-3-derived mediators possesses potent anti-inflammatory and pro-resolution properties and includes members of the D-series and E-series resolvins, protectins and maresins. Our laboratory has explored the potential salutary effects of these essential omega-3 fatty acids and omega-3-derived lipid mediators in the context of metabolic disorders associated with obesity. In this regard, our group has demonstrated that over-activation of pro-inflammatory lipid signalling pathways, in conjunction with a “resolution deficit” that prevents the return of adipose tissue to homeostasis, are directly responsible for the mild sub-clinical inflammation present in the adipose tissue of obese individuals. This unremitting and persistent inflammatory response is responsible for the development of an increasing number of obesity-related comorbidities with features of the metabolic syndrome, including insulin resistance and non-alcoholic fatty liver disease. Based on these findings, we have demonstrated that diets enriched with omega-3 fatty acids (docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids) are useful in reducing fat inflammation and in ameliorating insulin resistance and hepatic steatosis in obese animals. We have also demonstrated that transgenic *fat-1* mice expressing an omega-3 fatty acid desaturase, which allows the endogenous conversion of omega-6 into omega-3 fatty acids, are protected against the devastating metabolic consequences of obesity. Interestingly, we have provided evidence of a deficit in the formation of resolvin D1 and protectin D1, in diverse obese human fat depots. Moreover, we have experimentally demonstrated that these omega-3 derived lipid mediators counteract adipose tissue inflammation, insulin resistance and steatohepatitis by attenuating pro-inflammatory circuits and by switching recruited adipose tissue macrophages toward an anti-inflammatory, pro-resolving phenotype. All together, our findings provide unequivocal evidence that novel omega-3-derived pro-resolving lipid mediators are optimal templates for drug development to fight chronic inflammation and to prevent the metabolic complications associated with obesity.