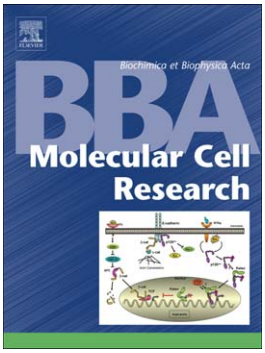

Pathologic endoplasmic reticulum stress induced by glucotoxic insults inhibits adipocyte differentiation and induces an inflammatory phenotype

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PATHOLOGIC ENDOPLASMIC RETICULUM STRESS INDUCED BY GLUCOTOXIC INSULTS INHIBITS ADIPOCYTE DIFFERENTIATION AND INDUCES AN INFLAMMATORY PHENOTYPE.

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ABSTRACT
Adipocyte differentiation is critical in obesity. By controlling new adipocyte recruitment, adipogenesis contrasts adipocyte hypertrophy and its adverse consequences, such as insulin resistance. Contrasting data are present in literature on the effect of endoplasmic reticulum (ER) stress and subsequent unfolded protein response (UPR) on adipocyte differentiation, being reported to be either necessary or inhibitory. In this study, we sought to clarify the effect of ER stress and UPR on adipocyte differentiation.
We have used two different cell lines, the widely used pre-adipocyte 3T3-L1 cells and a murine multipotent mesenchymal cell line, W20-17 cells. A strong ER stress activator, thapsigargin, and a pathologically relevant inducer of ER stress, glucosamine (GlcN), induced ER stress and UPR above those occurring in the absence of perturbation and inhibited adipocyte differentiation. Very low concentrations of 4-phenyl butyric acid (PBA, a chemical chaperone) inhibited only the overactivation of ER stress and UPR elicited by GlcN, leaving unaltered the part physiologically activated during differentiation, and reversed the inhibitory effect of GlcN on differentiation. In addition, GlcN stimulated proinflammatory cytokine release and PBA prevented these effects. An inhibitor of NF-kB also reversed the effects of GlcN on cytokine release. These results indicate that while ER stress and UPR activation is "physiologically" activated during adipocyte differentiation, the "pathologic" part of ER stress activation, secondary to a glucotoxic insult, inhibits differentiation. In addition, such a metabolic insult, causes a shift of the preadipocyte/adipocyte population towards a proinflammatory phenotype.

Keywords
Adipocyte differentiation, ER stress, inflammation.