



## Original Research Article

## Impact of AdipoR1 expression on breast cancer development

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## ABSTRACT

**Objective.** Adiponectin serum levels have been shown to be inversely correlated with breast cancer risk. The protein is believed to act through adiponectin receptor 1 (AdipoR1) and has been suggested to play an important role in cancer development. While AdipoR1 is known to be expressed in invasive tumors, its role in DCIS remains elusive. We therefore investigated AdipoR1 expression in both invasive and preinvasive breast cancer.

**Methods.** Tissue microarrays were established from paraffin-embedded archived tissues which contained 104 invasive breast cancers with adjacent preinvasive component (DCIS) as well as 96 preinvasive breast cancers. AdipoR1 expression was investigated by immunohistochemistry and correlated with clinical and tumor parameters.

**Results.** AdipoR1 was detected in stromal and epithelial components of both invasive and preinvasive breast cancer. However, stromal and epithelial immunoreactivity for AdipoR1 was significantly higher in invasive breast cancer compared to preinvasive DCIS ( $p < 0.001$  and  $p = 0.009$ ). Within DCIS, AdipoR1 expression was inversely correlated with tumor size ( $r = -0.238$ ,  $p = 0.033$ ). Menopausal status showed no influence on AdipoR1 expression.

**Conclusions.** The altered expression of AdipoR1 in invasive breast cancer compared to DCIS suggests that the receptor-binding protein adiponectin might exert growth inhibitory effects that are overcome in transformation of preinvasive to invasive breast cancer.

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## Introduction

There is now growing evidence for an insulin sensitizing and anti-atherogenic role of adiponectin, which is predominantly secreted by white adipose tissue: Serum levels of adiponectin have been reported to be significantly reduced in patients with cardiovascular disease and metabolic syndrome, respectively [1,2]. Furthermore, the insulin sensitizing effect of adiponectin could be demonstrated in an insulin resistant lipotrophic mouse model, which fully lacks serum adiponectin [3,4]. Administration of adiponectin to those mice significantly ameliorated hyperglycemia and hyperinsulinemia. Cloning of the adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) in 2003 allowed to closely investigate the actions of adiponectin *in vitro* and *in vivo*, respectively [5].

Recent evidence suggests that adiponectin might also act as a preventive agent with regard to several malignancies. Reduced adiponectin serum levels have been shown consistently to increase the risk for colorectal, endometrial, prostate cancer and breast cancer [6–9]. Regarding breast cancer this inverse correlation between adiponectin serum level and cancer risk has been reported to be independent of BMI, leptin and insulin-like growth factor-I concentrations [9].

*In vitro* studies even suggest direct antiproliferative effects of adiponectin on breast cancer cells [10,11]. AdipoR1 and AdipoR2 could be verified in breast cancer cells. Addition of adiponectin to different breast cancer cell lines resulted in growth inhibition, which in part can be explained by activation of the AMPK pathway [12–14]. It is believed that the anti-tumor effects of adiponectin are mediated to a greater extent through AdipoR1 than AdipoR2. Recently, Yamauchi et al. showed that the AMPK pathway, which seems to be crucial for the anti-tumor activity of adiponectin, is mainly activated through AdipoR1 [15]. Although expression of AdipoR1 has been verified in invasive breast tumors, data on the presence of this receptor in preinvasive lesions are lacking [13,16]. To further elucidate the role of AdipoR1 in breast cancer development and

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