

4<sup>th</sup> International Conference on

# CYTOPATHOLOGY & HISTOPATHOLOGY

August 29-30, 2018 | Boston, USA

## Significance of tissue expression and serum levels of angiopoietin-like protein 4 in breast cancer progression: Link to nf- $\kappa$ b /p65 activity and pro-inflammatory cytokines

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**Background:** The molecular mechanisms linking breast cancer progression and inflammation still remain obscure. The aim of the present study was to investigate the possible association of angiopoietin-like protein 4 (ANGPTL4) and its regulatory factor, hypoxia-inducible factor-1  $\alpha$  (HIF-1 $\alpha$ ), with the inflammatory markers nuclear factor kappa B/p65 (NF- $\kappa$ B /P65) and interleukin-1 beta (IL-1 $\beta$ ) in order to evaluate their role in inflammation associated breast cancer progression.

**Materials and Methods:** Angiopoietin-like protein 4 (ANGPTL4) mRNA expressions were evaluated using quantitative real-time PCR and its protein expression by immunohistochemistry. DNA binding activity of NF- $\kappa$ B /P65 was evaluated by transcription factor binding immunoassay. Serum levels of ANGPTL4, HIF-1 $\alpha$  and IL-1 $\beta$  were immunoassays. Tumor clinicopathological features were investigated.

**Results:** ANGPTL4 mRNA expressions and serum levels were significantly higher in high-grade breast carcinoma ( $1.47 \pm 0.31$  and  $184.98 \pm 18.18$ , respectively) compared to low-grade carcinoma ( $1.21 \pm 0.32$  and  $171.76 \pm 7.58$ , respectively) and controls ( $0.70 \pm 0.02$  and  $65.34 \pm 6.41$ , respectively), ( $p < 0.05$ ). Also, ANGPTL4 high/moderate protein expression was positively correlated with tumor clinicopathological features. In addition, serum levels of HIF-1 $\alpha$  and IL-1 $\beta$  as well as NF- $\kappa$ B /P65 DNA binding activity were significantly higher in high grade breast carcinoma ( $148.54 \pm 14.20$ ,  $0.79 \pm 0.03$  and  $247.13 \pm 44.35$  respectively) than their values in low grade carcinoma ( $139.14 \pm 5.83$ ,  $0.34 \pm 0.02$  and  $184.23 \pm 37.75$ , respectively) and controls ( $33.95 \pm 3.11$ ,  $0.11 \pm 0.02$  and  $7.83 \pm 0.92$ , respectively), ( $p < 0.001$ ).

**Conclusion:** ANGPTL4 high serum levels and tissue expressions in advanced grade breast cancer, in addition to its positive correlation with tumor clinicopathological features and HIF-1 $\alpha$ , could highlight its role as one of the signaling factors involved in breast cancer progression. Moreover, novel correlations were found between ANGPTL4 and the inflammatory markers, IL-1 $\beta$  and NF- $\kappa$ B/p65, in breast cancer, which may emphasize the utility of these markers as potential tools for understanding interactions for axes of carcinogenesis and inflammation contributed for cancer progression. It is thus hoped that the findings reported here would assist in the development of new breast cancer management strategies that would promote patients' quality of life and ultimately improve clinical outcomes. However, large-scale studies are needed to verify these results.

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