POSTER SESSION 6: Drug resistance and modifiers

P6.1

Not all TLE are the same- phosphorylation dependent different effects TLE3 versus TLE1 in adipose tissue and cancer

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Background: In mammals, there six Groucho orthologs, TLE 1-6 which may modulate MAPK and WNT signaling. They are considered to be structurally and functionally equivalent. We demonstrated that non-phosphorylatable TLE1 derivative suppresses tumorigenic effects induced by KRAS activation. TLE3 has a role in adipocyte differentiation and has been proposed as a marker for taxane sensitivity. Only 1 out of 8 possible MAPK phosphosites in TLE1 only one is divergent in TLE3. Here we studied the functional differences of TLE3 and TLE1 The possible effects of manipulation of the proximal putative phosphosite on these functions.
Methods: retroviruses expressing TLE1,TLE3 or TLE1 modified in the proximal phosphosite to TLE3 (TLE1-p3) or TLE3 modified to resemble TLE1(TLE3-p1) were transduced into preadipocytes and lung cancer cell line(a549). These cells were treated by either PPARgamma activator containing differentiation media or taxanes and analyzed for differentiation or cell death. mRNA array analysis was performed on adipocytes.
Results: TCGA analysis revealed differential relationship between TLE1,4 overexpression(correlated with poor survival) and TLE3 overexpression (no correlation to survival) in colon cancer. In pre- adipocytes TLE1 had higher effects on differentiation than TLE3, However TLE1-p3 influenced differentiation similarly to TLE3 and vice versa TLE3-p1 influenced differentiation similarly to TLE1. These changes were also reflected in analysis of mRNA arrays from these samples. In A549 cells transduction with TLE3 resulted in greater sensitivity to chemo then in TLE1 transduced cells which was lost when we used TLE3-p1(Fig1).In contrast to that TLE1-p3 effected taxane sensitivity similarly to TLE3.
Conclusion: There are some functional differences between TLE1 and TLE3 in diferntiation and cancer . The different functions may be modulated by a specific phosphorylation. Further mechanistic understanding of this proteins may provide new insightas to basic signal transduction events and provide novel targets for modulation of anticancer therapy.

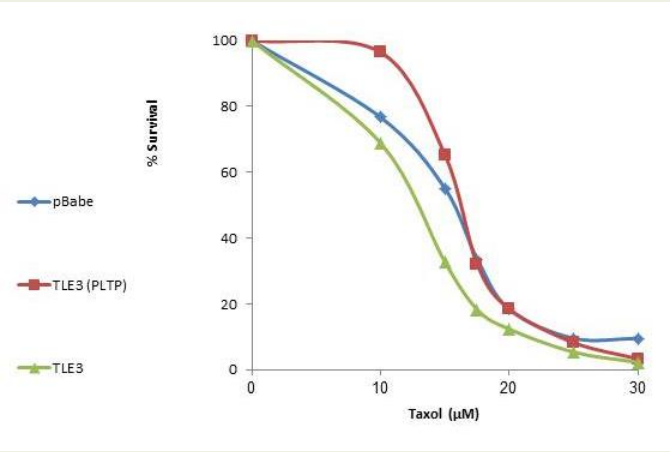

Fig 1 TLE3 transduction sentizes A549 cells to Taxanes while TLE3 modified in its proximal phosphosite to resemble TLE1 (TLE3 (PLTP) inhibits taxanes.