Epigenetic aberrations in disease pathogenesis

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Background:

Our recent clinical and experimental evidence suggest that autophagic suppression of liver cancer cells could contribute to tumor growth and metastasis, and its microenvironment is important for further prevention and therapeutics. The role of vasculature, inflammation, coagulation and immunity have been theoretically considered in improving the microenvironment of liver to prevent and cure cancer. Thus, our attention is given to the potential modulation of molecular events (targets and modulators) in regulating autophagy of hepatoma cells. In the past two years, we have particularly studied the miR-135a-promoted progression of hepatocellular carcinoma (HCC) in association with relatively high FVII expressed in tumor tissues (Topic I).

We also investigated the epigenetic and molecular underpinnings of Golli myelin basic protein (Golli-MBP) for disease severity in childhood atopic dermatitis (AD). Among the globally hypomethylated loci in immune cells of AD children, we identified two CpG clusters within the *Golli* locus of the MBP promoter which negatively associated with golli-MBP gene expression as well as correlated with disease severity (Topic II).

Research Topic I:

The FVII/PAR2-elicited suppression of autophagy is mediated by miR-135a over-expression in association with tumor malignancy.

We have demonstrated a significant positive correlation between the expression of FVII and miR-135a in tumor specimens and a significant inverse association between miR-135a and the autophagic protein ATG14. Furthermore, HCC patients with high levels of miR-135a while compared with the adjacent normal area had drastic worse disease-free survival than those with low levels of miR-135a in tumors.

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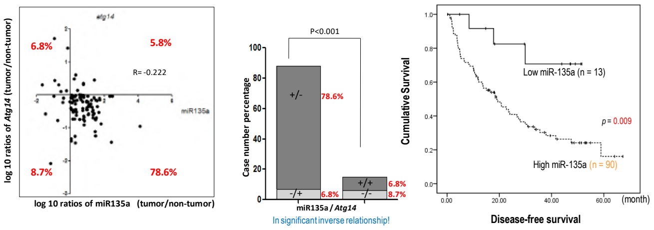

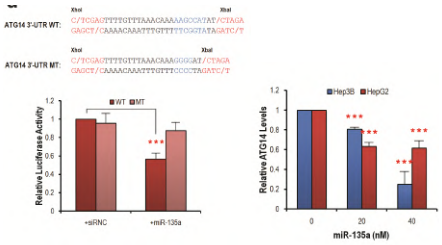

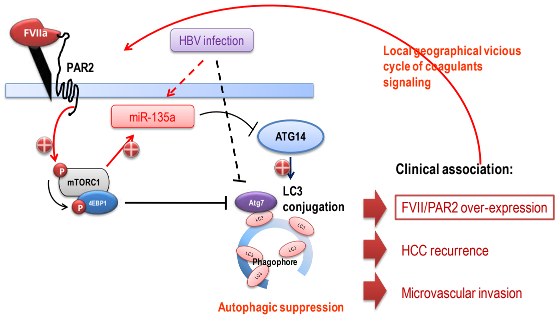

Scheme showing miR-135a transduces the FVII coagulation signal to suppress autophagy with a mTOR-dependent manner in HCC.

Our results indicated that FVII/PAR2 signaling through miR-135a overexpression via at least mTOR activation has potent effects on the migration and invasion of hepatoma cells *in vitro* and clinically associated with microvascular invasion and tumor recurrence of HCC.

Research Topic II:

Methylation loss in the *golli-mbp* locus is an epigenetic factor associated with disease severity of childhood AD.

DNA methylation in the cg27400313 cluster was found to be negatively correlated with disease severity but showed no significant correlation with IgE levels after age adjustment in AD children.

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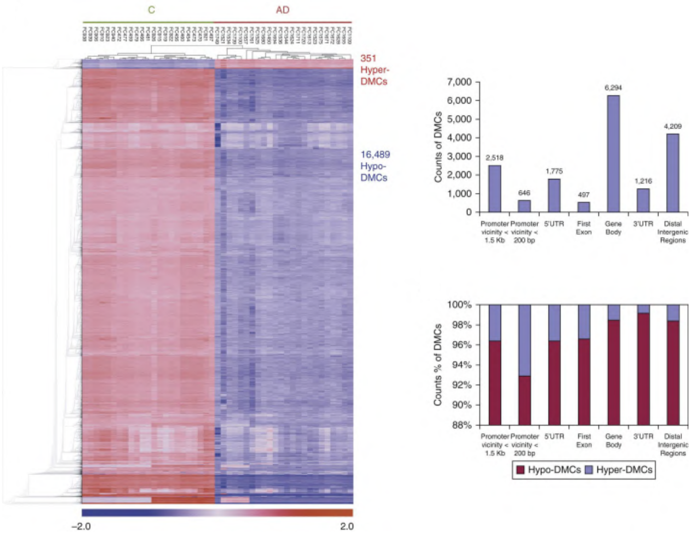
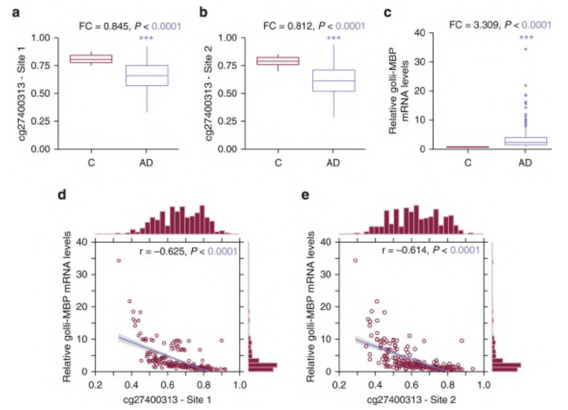


Distinctive patterns of global DNA hypomethylation in peripheral blood leukocytes of patients with childhood AD.



DNA methylation and gene expression analysis for golli-MBP. (a) Site 1 at cg27400313 methylation differential analysis between 224 patients with AD and 44 Cs. (b) Site 2 at cg27400313 methylation differential analysis between 224 patients with AD and 44 Cs. (c) Golli-MBP expression differential analysis between 224 patients with AD and 44 Cs. (d) Association between cg27400313 site 1 methylation levels and golli-MBP expression of the validation cohort. (e) Association between cg27400313 site 2 methylation levels and golli-MBP expression of the validation cohort. Significance is established at an adjusted P-value of 0.05 (∗∗∗P < 0.0001). AD, atopic dermatitis; C, control subject; FC, fold change.