2-LBS-31 Late-Breaking Session

Drug discovery screening based on epigenetic control of COPD – Benserazide inhibits the prothymosin α-H1 histone interaction

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Anti-cholinergic inhibitors have been used for the treatment of chronic obstructive pulmonary disease (COPD). Because of their side effects, there is a big demand for new type of drugs. Su et al., (Nature Commun, 2013) has proposed a hypothesis that prothymosin α (ProTα) upregulated in emphysema patients binds to histone H1 and eliminates the histone deacetylase (HDAC) bound to H1, leading to an epigenetic upregulation of matrix metalloprotease (MMP) gene expression, which may cause pulmonary cell damage. In addition, Borge et al., (Nature, 2018) demonstrated that ProTα binds to H1 at a picomolar level of Kd value. Based on these reports we attempted to find inhibitors of ProTα-H1 interaction by use of homogenous time-resolved fluorescence (HTRF). Using an existing drug compound library (～2300 compound), we obtained benserazide, which inhibits the interaction by 70% at 30 μM. Although it is under investigation whether benserazide has beneficial actions against the toxicity of cigarette smoking extract (CSE) or its constituents, here we will present following findings, as follows; 1) ProTα gene expression is very high in A549 lung cancer cells, 2) the treatment with siRNA ProTα gene down-regulated the expression of MMP2 gene as well as ProTα gene in A549 cells, 3) benserazide alone has no action, but it deteriorated the CSE-induced damage of survival activity of A549 cells, 4) from the RNAseq analysis of lung, which has been treated with CSE (i.v,) for 6 weeks, it was found that some candidate genes involved in CSE-induced toxicity and its reversibility by benserazide.