Functional pan-universality of the age-related regulatory elements ASE and AIE, and development of age dimension technology

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Blood coagulation activity in humans increases with advancing age. This is apparently due to the age-related increase in disparity between pro-coagulant and anticoagulant activities, and may contribute to thrombosis and cardiovascular diseases in elderly. Recently we reported the first age-related regulatory mechanisms of gene expression and its fundamental universality (Science 1999; 285: 739-43; J. Biol. Chem. 2002; 277: 4532-40) using human factor IX (hFIX) and anticoagulant human protein C (hPC) gene. We showed that ASE is essential for the age-related stability of hFIX and hPC gene expression and AIE is essential for age-related increase of hFIX gene (hPC gene lacks AIE). We also showed that the conversion from the age-stable pattern of hPC gene expression to age-increase pattern can be done with AIE.

Here we tested whether or not the age-related regulatory mechanisms universally function with totally unrelated, heterologous genes. A set of hFIX minigene expression vectors with a CMV promoter with and without ASE were constructed. These constructs showed similar transient expression activities in HepG2 cells. However, transgenic mice carrying these minigenes showed markedly different expression patterns. Animals carrying hFIX minigene without ASE showed age-unstable decline in hFIX expression in 8-9 months of age. In contrast, minigenes with ASE showed stable expression over 10 months of age (end of experiment). These results successfully supported that the age-regulatory mechanisms, which were originally found with blood coagulation factor genes, function with the CMV promoter. Animal testing of ASE and AIE combination in animals is in progress.

These observations lead us to developing Age Dimension Technology (ADT), a novel field of applications of new knowledge obtained through these studies.

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