東北大学グローバルCOE

Network Medicine 創生拠点

NM高等教育セミナー

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「Modulating epigenetics to treat the first,and most prevalent, inherited human disease」

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The human globinopathies (α- and β-thalassemia and sickle cell disease [SCD]) are the most prevalent human diseases, and yet even after 60 years since defining the molecular basis for SCD, we still have no uniformly effective, safe treatment. While the field has known for decades that elevated expression of γ-globin ameliorates SCD symptoms and pathophysiology, no γ-globin-specific activating transcription factor protein has been identified. In pursuing an alternative strategy, we discovered a γ-globin gene repressor in 2002. We recently described the molecular components of a γ-globin gene repressor, and discovered that it consists of a collection of complexes all of which are repressors. The DRED "core" contains TR2 and TR4, the orphan nuclear receptors that together bind to DNA, the maintenance DNA methylase DNMT1, and LSD1, the H3K4- and H3K9-specific histone demethylase. This core complex then associates with a variety of other epigenetic modifier enzymes. We asked whether forced expression of TR2+TR4 in erythroid cells would exert a phenotype on γ-globin expression, and remarkably, found that in an <I>in vivo</I> mouse model of SCD, γ-globin synthesis could be dramatically induced. We also asked whether a small molecule inhibitor or shRNA-encoded lentivirus that blocked LSD1 activity would effect γ-globin synthesis; treatment of CD34+ human hematopoietic stem cells induced to differentiate into erythroid cells with either agent led to a 4-7-fold induction of γ-globin mRNA and protein. These data suggest that targeting either TR2/TR4 or the LSD1 histone demethylase could result in a safe and effective treatment for SCD and/or β-thalassemia.

本セミナーは医学履修課程特別セミナーを兼ねています。受講学生は履修振替簿を持参し、セミナー修了後にサインを受けること。聴講は自由大歓迎です。学部生の皆さんもぜひどうぞ。

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