Researcher discovers epigenetic links in cell-fate decisions of adult stem cells

July 9 2012, By Brianna Deane

(Medical Xpress) -- The ability to control whether certain stem cells ultimately become bone cells holds great promise for regenerative medicine and potential therapies aimed at treating metabolic bone diseases.

Now, UCLA School of Dentistry professor and leading cancer scientist Dr. Cun-Yu Wang and his research team have made a significant breakthrough in that direction. The scientists have discovered two key epigenetic regulating genes that govern the cell-fate determination of human bone marrow stem cells.

Wang's new research is featured on the cover of the July 6 issue of *Cell Stem Cell*, the affiliated journal of the International Society for Stem Cell Research.

The groundbreaking study grew out of Wang's desire to better understand the epigenetic regulation of stem cell differentiation, in which the structure of genes is modified while the sequence of the DNA is not. He and his team found that KDM4B and KDM6B, two gene-activating enzymes, can promote stem cells' differentiation into bone cells by removing methyl markers from histone proteins. This process occurs through the activation of certain genes favoring a commitment to one lineage and the concurrent deactivation of genes favoring other lineages.

The findings imply that chemical manipulation of these gene-activating

enzymes may allow stem cells to differentiate specifically into bone cells, while inhibiting their differentiation into fat cells. The group's research could pave the way toward identifying potential therapeutic targets for stem cell–mediated regenerative medicine, as well as the treatment of bone disorders like osteoporosis, the most common type of metabolic bone disease.

"Through our recent discoveries on the lineage decisions of human bone marrow stem cells, we may be more effective in utilizing these stem cells for regenerative medicine for bone diseases such as osteoporosis, as well as for bone reconstruction," Wang said. "However, while we know certain genes must be turned on in order for the cells to become bone-forming cells, as opposed to fat cells, we have only a few clues as to how those genes are switched on."

The research group, through its study of aging mice, found that the two enzymes KDM4B and KDM6B could specifically activate genes that promote stem cell differentiation toward bone, while blocking the route toward fat.

"Interestingly, in our aged mice, as well as osteoporotic mice, we observed a higher amount of silencing histone methyl groups which were normally removed by the enzymes KDM4B and KDM6B in young and healthier mice," Wang said. "And since these enzymes can be easily modified chemically, they may become potential therapeutic targets in tissue regeneration and treatment for osteoporosis."

"The discovery that Dr. Wang and his team have made has considerable implications for craniofacial bone regeneration and treatment for osteoporosis," said Dr. No-Hee Park, dean of the UCLA School of Dentistry. "As a large portion of our population reaches an age where osteoporosis and gum disease could be major health problems, advancements in aging-related treatment are very valuable."

Professor Wang holds the No-Hee Park Endowed Chair in Dentistry at the UCLA School of Dentistry, where he is also chair of the division of oral biology and medicine and the associate dean for graduate studies.

The study was supported by grants from the National Institute of Dental and Craniofacial Research.

Provided by University of California, Los Angeles