OMICS Group Conferences
Accelerating Scientific Discovery

International Conference and Exhibition on
Neurology & Therapeutics

May 14-16, 2012 Embassy Suites Las Vegas, USA

The gene encoding for KLHL9 is frequently deleted in high-grade glioma with a mesenchimal signature

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High-Grade Glioma (HGG), including astrocytoma grade III and IV, are the most common brain tumors and have a poor prognosis, with an average of survival of 12 months post diagnosis. The most aggressive subtype of HGG is characterized by expression of 'mesenchymal genes', driven by aberrant activation of several transcription factors, such as C/EBPbeta and delta. Despite the growing availability of data and the identification of clinically relevant molecular subtypes within HGG, the genetic alteration contributing to the different subtypes remain largely unknown.

Integration of copy number alteration data and regulatory network analysis lead to to the identification of the deletion of the KLHL9 locus, an adaptor of Cullin3-based E3 ligases involved in ubiquitination processes, which accounts for the majority of mesenchimal and worst prognosis samples in glioblastoma multiforme. Deletion of KLHL9 deprives glioma cells of a specific ubiquitin-mediated degradation activity towards C/EBPbeta and delta, resulting thereby in the aberrant accumulation of these two transcription factors. Restoration of KLH9 in glioma cells harboring homozygous deletion of the KLHL9 gene triggered ubiquitin-mediated, proteasome-dependent destruction of the two transcription factors, promoting cell cycle arrest. Studies in an independent cohort of HGG patients confirmed that KLHL9 was deleted in 67% of the poor prognosis cases and only in 33% of good prognosis ones.

Taken together, these findings indicate KLHL9 as the most frequently altered gene promoting the aggressive mesenchymal subtype of HGG.

Biography

Dr. Lee has completed his Ph.D at the age of 26 years from Seoul University and postdoctoral studies from Penn University School of Medicine. He is the director of Niobox, a premier Bio-Soft service organization. He has published more than 100 papers in reputed journals and serving as an editorial board member of reputed journals.

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