Cancer Metastasis of Hepatocellular Carcinoma

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After obtaining his BSc in Biochemistry at Imperial College, University of London UK (1993), Yick-pang Ching continued his PhD training in Department of Biochemistry at University of Dundee, Scotland UK (1997). He then returned to Hong Kong and had his first post-doctoral training in Hong Kong University of Science and Technology for three years. After that, he moved to Institute of Molecular Biology at The University of Hong Kong, working as postdoctoral fellow for another three years. Since 2003, he has been appointed as Research Assistant Professor in the Department of Pathology and Biochemistry at the same university.

His researches mainly focus on how the dysregulation of small Rho GTPase pathway contributes to pathogenesis of liver cancer. In 2003, he has identified a novel negative regulator of Rho GTPases, designated deleted in liver cancer 2 (DLC2), which has been shown to be frequently underexpressed in liver cancer samples. DLC2 is a RhoGAP protein, which downregulates RhoA and Cdc42 activity. Expression of DLC2 RhoGAP domain can effectively inhibit the transformation of fibroblast cells induced by dominant active Ras, suggesting that DLC2 is also a putative tumor suppressor gene.

Liver cancer (hepatocellular carcinoma, HCC) is one of the most common cancers worldwide and is the third most common cancers in Southeast Asia and Hong Kong. So far, the overall prognosis of HCC is unsatisfactory due to the high incidence of recurrence and intrahepatic metastasis. It is therefore a high priority to unravel the molecular mechanisms underlying the metastasis of HCC so that better treatment modalities can be designed.

Small Rho GTPase family, which belongs to Ras GTPase superfamily, regulates the actin cytoskeleton, cell migration, cell cycle progression, gene transcription and apoptosis. The most well characterized Rho GTPase family member are RhoA, Rac1 and Cdc42. They exist in an active, GTP-bound and an inactive, GDP-bound form. The cycling between the GDP to GTP form is positively regulated by guanine exchange factor (GEF) and is negatively regulated by GTPase activating protein (GAP). When the Rho GTPase is in its active GTP-bound form, it will bind to their specific effectors and activate the downstream signaling pathways.

Rho GTPases have been reported to play an important role in invasion and metastasis of cancers. RhoA has been shown to regulate the formation and maintenance of cadherin-dependent cell-cell contacts and that constitutes one of the major regulatory mechanisms for cell attachment. The human deleted in liver cancer 1 (DLC1) gene that was first cloned from HCC by PCR-based subtractive hybridization technique is localized at chromosome 8p21-22. DLC1 is epigenetically silenced by promoter DNA methylation and loss of DLC1 promotes cell invasion by enhanced RhoA activity. By sequence homology search, the human homologue of DLC1, named DLC2, was identified in chromosome 13q12. This region was found to have a high frequency of loss of heterozygosity in HCC. Similar to DLC1, DLC2 also downregulates RhoA and Cdc42 activity and its transcript are underexpressed in HCC. DLC2 suppresses cell transformation by inhibition of RhoA activity. These findings suggest that downregulation of RhoA is critically involved in HCC formation. Thus it is of great interest to further understand the role of small Rho GTPase pathways in HCC metastasis.