Human Papillomaviruses and Cancer : Mechanistic Insights

Dr. Peter M. Howley

Shattuck Professor of Pathological Anatomy
Chair, Department of Pathology
Harvard Medical School, USA

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Howley博士はハーバード大学医学部のDept. of PathologyのChairであり、パピローマウイルスによる子宮頸癌の発癌機構およびウイルス発癌研究の世界的なリーダーです。その功績により、米国科学アカデミーの会員に選ばれています。パピローマウイルス研究を通してユビキチンリガーゼE6APを発見し、ユビキチン－プロテアソーム系の病態生理学的意義を世界で初めて明らかにしたことでも有名です。近年、子宮頸癌のみでなく、パピローマウイルス感染と口腔咽頭癌との関係も注目されています。今回は、最新のデータもふまえてご講演して頂く予定です。皆様、是非ご参加くださいますようお願い申し上げます。

Abstract

The subgroup of human papillomaviruses that is associated with anogenital and certain upper airway cancers encode two oncoproteins E6 and E7, which are invariably expressed in the HPV positive cancers. The E7 protein functions in cellular transformation, at least in part, through interactions with pRB and the other pRB related "pocket proteins". E7 also contributes to genomic instability by affecting centrosome duplication. The major target of the E6 is p53; E6 targets the ubiquitylation and degradation of p53 by directing the E6AP ubiquitin ligase to p53. E6 has also been shown to activate the expression of the catalytic subunit of cellular telomerase. Several lines of evidence suggest that E6 and E7 have yet additional targets important to their oncogenic potential and their ability to cause genomic instability.

The viral E6 and E7 oncoproteins are under the control of the viral E2 gene, which is a critical regulatory gene encoded by the papillomaviruses that has roles in viral transcription, DNA replication and genome maintenance in dividing cells. One important function of the E2 protein is its ability to repress the viral LCR promoter responsible for expression of the E6 and E7 oncogenes. We have recently conducted a whole genome siRNA screen to identify the cellular genes and pathways involved in E2 mediated transcriptional repression. We have confirmed that Brd4, a major E2 interacting protein, has a role in this repression function and show that there are also Brd4 independent pathways that function in an additive manner with Brd4.

There is a second spliced E2 isoform in which a short amino acid segment of E8 is spliced to the C-terminal DNA binding/dimerization domain of E2. This E8^E2 protein can also function as a transcriptional repressor but does so in a manner distinct from that of the full length protein. We have conducted proteomic and genetic studies to determine the mechanism by which this second form of E2 functions as a transcriptional repressor.

A major advance in the human viral oncology field has been the development of an effective preventive vaccine for some of the HPV types associated with cancer. To date however, there are no specific HPV therapies or therapeutic strategies for HPV infections. Possibilities could include therapeutic vaccines or small molecule drug strategies. Two potential drug targets for the papillomaviruses would be E6 and E2. Interfering with E6 function in cells expressing the viral E6 and E7 oncoproteins could lead to cellular apoptosis. E2 is a critical viral regulatory protein involved in viral transcription, viral DNA replication and viral genome persistence. By exploring the cellular mechanisms by which E2 functions and the cellular molecule through which it mediates its various functions we hope to identify potential targets for small molecule inhibitor/drug development.

(References: Howley et al., Cell 75, 495-505, 1993., Mol Cell 6: 409-19, 2000, Cell 117: 349-60, 2004., JVI 80: 8909-19,2006., JVI 81: 9612-22, 2007., JVI 83: 8683-92, 2009., MCB 29: 5094-103, 2009)

担当：医学研究科・感染症センター・微生物学分野　堀田博
連絡先：微生物学分野　勝二郁夫（内線5501) E-mail: ishoji@med.kobe-u.ac.jp
シグナル伝達GCOE事務局　丸山真由美 (内線5200）E-mail: gcoestm@med.kobe-u.ac.jp