Diagnostic Technology

Map kinase kinase kinase kinase 3 (MAP4K3) as a biomarker and therapeutic target for autoimmune disease, cancer, inflammation and IL-17-associated disease

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NF-κB is a major transcription factor that regulates genes responsible for cell survival, growth and proliferation. T cell receptor (TCR) engagement induces NF-κB activation, which is involved in the host defence against infection and the development of inflammation, cancer and autoimmunity. PKC-θ activation requires its phosphorylation at T538. The kinase PDK1 interacts with PKC-θ and phosphorylation of PKC-θ at T538 is defective in PDK1-deficient T cells. Thus, PDK1 has been proposed to directly phosphorylate PKC-θ at T538, although no clear evidence exists that PDK1 directly phosphorylates PKC-θ in vitro. Furthermore, the observation that PDK1 can be activated only by CD28, but not TCR signaling, further rules out the possibility that PDK1 is the direct kinase for PKC-θ activation induced by TCR signaling. Thus, the kinase that directly activates PKC-θ during T cell activation remains elusive.

The invention relates to a method for identifying a therapeutic agent for treating a Germinal Center Kinase (GCK)-Like Kinase (GLK)-mediated disease. The method comprises detecting a modulation of GLK-mediated signal transduction by a test compound, in which the detecting step comprises: a) culturing GLK-expressing cells in the presence of the test compound, wherein said modulation is detected by measuring the expression level of GLK transcripts or protein, the amount of IL-17A produced or the activity of NF-κb; or b) allowing a GLK protein to react at the presence of ATP with a substrate thereof in the presence of the test compound, wherein said modulation is detected by measuring the amount of ADP produced, the amount of ATP consumed and/or the amount of the substrate being phosphorylated; or c) culturing GLK-expressing cancer cells in the presence of the test compound, wherein the modulation is detected by measuring migration/invasion/wound healing of said cancer cells; or d) allowing a GLK protein to interact with a substrate protein thereof in the presence of the test compound, wherein said modulation is detected by measuring the interaction between the GLK and the substrate protein; and e) comparing said modulation in the presence of the test compound with a control identifies a therapeutic agent for treating a GLK-mediated disease. The invention relates to a method for detecting the presence and/or severity of a Germinal Center Kinase (GCK)-Like Kinase (GLK)-mediated disease.

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Methods for Detecting Hepatitis B Virus Surface Gene Non-Sense Mutations

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Hepatocarcinogenesis of HBV-related HCC is believed to be a “hit-and-run” event as most of the surgically removed cancerous HCC tissues contain rare, if any, freely replicative viruses. Therefore, if certain viral mutations were assumed to be responsible for initiation of the oncogenic process, one could not identify them because the mutant viruses should have been lost in the subsequent steps of hepatocarcinogenesis.

Gene S of hepatitis B virus (EBV) is the gene that codes for the surface antigen (HBsAg). The HBsAg gene is one long open reading frame but contains three in frame “start” (ATG) codons that divide the gene into three sections, pre-S1, pre-S2, and S. Because of the multiple start codons, polypeptides of three different sizes called large S, middle S, and small S (pre-S1+pre-S2+S, pre-S2+S, and S, respectively) are produced. During the course of chronic hepatitis B infection, the viral genome would frequently develop mutations. These mutations represent the attempt of the virus to escape from host immune-surveillance.

The present invention discloses a method for in vitro detection of the presence of a C-terminal truncation mutation of a hepatitis B virus (HBV) surface (S) gene encoding a small S protein in an isolated nucleic acid sample is disclosed. An in vitro diagnostic kit for use in the aforementioned method is also disclosed.

Since there are multiple HBV S gene non-sense mutations, and they could co-exist in one tumor, using specific primer sets developed in the present invention can detect the HBV S gene non-sense mutations directly, instead of direct sequencing the genes one by one. For screening large amount of specimens, the technique disclosed can save time, money and manpower.

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Use of 5-methoxytryptophan as diagnostic agent of inflammatory diseases

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Inflammation is caused by excessive and inappropriate innate immune system activity. Cellular and molecular factors responsible for inflammation in the diverse health problems and diseases are complex and not necessarily identical. The inventors have recently identified by comparative metabolomics a novel tryptophan metabolite, 5-methoxytryptophan (5-MTP) as a cytoguardin. L-tryptophan is an essential amino acid which serves not only as building block of protein synthesis but also as substrate for producing diverse metabolites some of which, such as serotonin, melatonin and kynurenine play well-recognized important physiological roles. 5-MTP is produced from L-tryptophan via a novel pathway. 5-MTP inhibits proinflammatory mediator-induced COX-2 expression in fibroblasts and cancer cells and reduces cancer cell migration and invasion and cancer metastasis in a xenograft model.

Since COX-2 is a major mediator of inflammation and overexpressed in diverse inflammatory disorders including sepsis, inventors' previous works have indicated that 5-MTP play an important role in inflammatory diseases such as sepsis and systemic lupus erythematosus (SLE). The research team further developed the diagnostic method disclosed in this invention

The present invention discloses a diagnostic method for inflammatory diseases, and the diagnostic kit used in the method. The diagnostic method of present invention comprises the use of a novel tryptophan metabolite, 5-methoxytryptophan (5-MTP), as a diagnostic biomarker of inflammation. The present invention specially provides a highly specific competitive ELISA to measure 5-MTP level in human serum for gauging occurrence and severity of inflammatory diseases, including sepsis and systemic lupus.

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