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The hepatocyte growth factor prevents hepatotoxicity induced by the administration of therapeutically suprapharmacological doses of isoniazid and rifampicin in a model of murine multidrug resistant pulmonary tuberculosis

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Tuberculosis (TB) is a worldwide health problem. The World Health Organization (WHO) informed that there were 9.6 million new active cases and 1.5 million deaths during 2014.Although TB can be controlled and cured by chemotherapy, treatment usually requires four specific antibiotics during 6 months, and the most efficient drugs isoniazid (INH) and rifampicin (RIF) frequently produce liver damage. This long and toxic effect of TB treatment produces significant compliance problems. The consequence of this is disease recurrence and the arising of multi drug resistant (MDR) strains. During the last years MDR have increased their frequency, in 2014 MDR TB afflicted around 480,000 people worldwide and produced 190,000 deaths. Treatment of MDR-TB is resource intensive and requires second line drugs which are more expensive, toxic, and less effective than primary drugs. These problems have motivated the search for new drugs and treatment strategies. MDR strains have a drug-resistance threshold, high concentrations of INH and RIF can kill MDR bacilli but these suprapharmacological doses of antibiotics produce severe liver damage. Hepatocyte growth factor (HGF) is a multitask growth factor that stimulates both ant apoptotic and antioxidant responses that counteract the toxic effects of drug metabolism in the liver. We previously showed that recombinant HGF (iv) prevented all the harmful effects of INH and RIF by increasing the activation of Erk1/2 and PKCδ signaling pathways and glutathione (GSH) synthesis. In this study BALB/c mice were infected intra-tracheally with a high dose of MDR clinical isolate resistant to all primary drugs, after 3 months of infection when mice suffered extensive progressive pulmonary TB animals were treated with suprapharmacological doses of INH and RIF by intragastric or intra-tracheal route in combination with recombinant HGF (IP). Particularly the intratracheal treatment produced a significant decrease of pulmonary bacillary loads in coexistence with less tissue damage in the lungs (pneumonia) and in the liver (esteatosis, necrosis). This is a novel scheme of treatment of MDR-TB that uses high doses of conventional chemotherapy but with the addition of a liver protector which is HGF.

Biography

Rogelio Hernández-Pando is working as a Faculty member of Experimental Pathology Section working under Department of Pathology at National Institute of Medical Sciences and Nutrition, México. Research experience includes various programs, contributions and participation in different countries for diverse fields of study. His research interests mainly include multidrug resistant pulmonary tuberculosis, Tuberculosis (TB).

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