Chemically Modified Glucans as Perspective Immunostimulators

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Glucans are known as effective immunostimulators, but water-insolubility of these compounds restricte their effective usage in clinical medicine. Chemical modification (carboxymethylation) of beta-1,3-glucan (produced by Chemical Institute, SAS, Bratislava, Slovakia) was followed by formation of water-soluble compounds which are perspective for treatment of several diseases accompanied by immunodeficiency. Three fractions of carboxymethylglucan (CMG) with different molecular weights were shown to have a prominent immunostimulating effect, mainly macrophage stimulation. We proposed a positive therapeutic effect of CGM in treatment of lysosomal storage syndrome in human like mucopolysaccharidosis (MPS). An animal model of MPS was introduced by Constantopoulos et al. by administration of suramin in rats. Decrease of some lysosomal enzymes activity (acid phosphatase and β-glucuronidase) and concomitant pathological changes in liver, spleen, kidney and lung were noticed after suramin administration that mimiced the features of MPS. We used CMG in vivo in model of lysosomal storage disease induced by suramin in mice.

Methods. One group of CBA mice received a single suramin administration in a dose of 250mg/kg via tail vein and was decapitated 48 h afterwards. Another group of mice received CGM as a single dose of 25 mg/kg and was decapitated 48 h afterwards. The third group received CMG and 48h afterwards - suramin in doses mentioned above and was decapitated 48h after the last administration. Intact CBA mice served as a control. Lysosomal enzymes activity was measured against fluorogenic substrates on Perkin-Elmer fluorometer.

Results. CMG administration was followed by macrophage stimulation in spleen (according to β-galactosidase activity - a marker enzyme of macrophage), and the most prominent effect was observed in a model of CMG + suramin (4^{th} day after CMG administration, suramin had no effect on this enzyme in spleen). Mannan and glucan were shown to increase a number of sinusoidal liver cells (mainly, macrophages).

Protective effect of CMG second fraction against lysosomal storage syndrome development in mice was shown. Among lysosomal enzymes studied suramin significantly decreased N-acetyl-β-D-hexosaminidase (β-HEX) activity in liver and spleen. There were no changes of this enzyme in lung and brain. Pretreatment by CMG normalized the enzyme activity in liver and spleen. Suramin induced also paradoxical increase of β-D-galactosidase activity in lung, and CMG normalized the enzyme activity. Stability test revealed increased labilization of lysosomes by suramin and CMG had not protective effect

Consequently CMG pretreatment prevented the development of lysosomal storage syndrome in mice in that organs which were affected by suramin administration. There was no decrease of lysosomal enzymes activity under influence of suramin in GMG-pretreated mice.

We can conclude that macrophage stimulator CMG can be used as a new perspective immunostimulator for treatment of lysosomal storage syndrome. It may be also useful in treatment not only MPS, but also other inborn lysosomal diseases with defect of different lysosomal enzymes.