Mesangial Cell Lines as Models for the Study and Treatment of Diabetic Tissue Complications

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Technology description

Description

The present invention relates to a model system for simulating diabetes. More specifically, the present invention relates to an isolated and stable clone of cells which exhibit characteristics of diabetic cells for use in testing anti-diabetic drugs, and the pathogenesis of diabetic nephropathy. Further, the present invention relates to the use of a stable, permanent clone of mesangial cells which underexpresses GLUT1 mRNA and protein and which can be used therapeutically. The present invention provides a new in vitro model system for simulating diabetes in the mesangial cell (MC) and a gene therapy for diabetic tissue complications. More specifically, the present invention provides an isolated and stable clone of mesangial cells (MCS) which exhibit characteristics of diabetic cells and overexpress GLUT1. The present invention further provides a stable, permanent clone of mesangial cells which underexpress GLUT1 mRNA and protein which can be used therapeutically. In accordance with the present invention, three stable, cloned mesangial cell lines have been developed: mesangial cell clones engineered to express the reporter gene for beta-galactosidase (control cell line) at high levels, to overexpress GLUT1, or to underexpress GLUT1. In addition, an effective new antisense GLUT1 DNA construct which downregulates GLUT1 in target cells, protecting them from the adverse effects of diabetes has been developed. Overexpression of GLUT1 in mesangial cells, as for example the MCGT1 clone, reproduces the diabetic phenotype in these cells, without any increase in extracellular glucose concentration. The MCGT1 cells behave like diabetic cells, even in the absence of elevated extracellular glucose concentrations. The overexpressing GLUT1 cell line, along with the control MCLacZ cell line, are used for testing the effectiveness of new drugs expected to have therapeutic benefit for the kidney in diabetes and also to identify drugs that could have a harmful effect on the kidney in diabetes. These stably transduced cell lines will also be useful for studying the pathogenesis of diabetic kidney disease as it relates to excess glucose assimilation by the mesangial cell. Underexpression of GLUT1 in mesangial cells, as for example the MCGT1AS clone, protects them from the harmful effects of high glucose in the diabetic range. Applicants have therefore developed an antisense-GLUT1 DNA expression construct for this purpose, called pWZLneoGLUT1AS, which can be transferred to mouse, rat, or human cells via the MoMuLV retrovirus. The MCGT1AS cells produced by transduction with the pWZLneoGLUT1AS expression construct, are shown to be protected from the adverse effects of high

extracellular glucose concentrations. In addition, DNA constructs developed to transduce mesangial cells, can also be used to transduce other cells in vitro or in vivo, whether via a viral vector or with modifications by other means, for therapeutic or nontherapeutic purposes.

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