

Novel reporter assays for genotoxicity and oxidative stress

Market Sector: genotoxicity testing, drug development

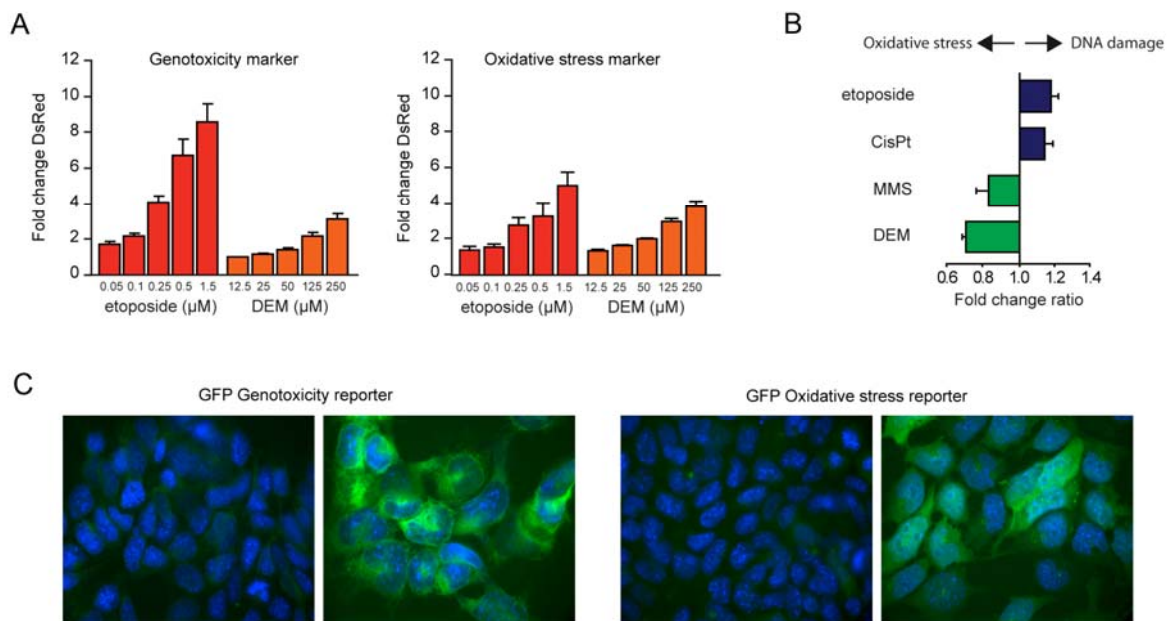


Fig. 1 Fluorescent reporter systems for assessment of genotoxicity or oxidative stress in mouse embryonic stem (mES) cells. Promoters of selected biomarker genes were linked to red fluorescent DsRed-Express2 or green fluorescent GFP and stably integrated in mES cells. (A) Sensitive detection of genotoxicity (etoposide) and/or oxidative stress (diethyl-maleate [DEM]) induction by flow cytometry. (B) Comparison between two different red fluorescent reporters allows accurate discrimination between DNA damage or oxidative stress. (C) Sensitive microscopy techniques and live cell imaging allow intracellular visualization and quantification of genotoxicity and oxidative stress induction.

Industry yearly develops a large number of new chemical compounds for a wide range of applications. These compounds may react with various cellular structures and organelles, including DNA, proteins and lipids and affect multiple cellular processes. Reactivity towards cellular DNA of exposed organisms may cause mutations, affect genome stability and may ultimately lead to the development of genetic diseases and cancer. Compound exposure may also result in the formation of reactive oxygen species, which have also been implicated in cellular dysfunctioning, generation of mutations and aging.

Scientists at the Leiden University Medical Center and Leiden University have now identified genes that can serve as biomarkers for exposure to genotoxic or oxidative stress. Fluorescent reporters based on these biomarker genes were incorporated into highly sensitive mouse embryonic stem (mES) cells, providing a unique, highly sensitive system that can provide insights into the primary mode of toxicity of tested agents. Activation of the reporters can rapidly be assessed by flow cytometry or automated high content imaging in 96-wells microtiter plates allowing high throughput screening, making it an attractive assay for use in early stages of drug development.

Keywords

Biomarker, genotoxicity testing, DNA damage, oxidative stress, reporter system, embryonic stem cells.

Current study

- Various other mES reporter cell lines specific for distinct toxicity pathways are being developed.
- The capacity to metabolically activate pro-genotoxic compounds is being integrated in the mES cell system.
- Procedures for ES cell differentiation are being applied to study tissue-specific effects of (geno)toxic compounds.

Commercial Partner Sought

Chemical and pharmaceutical companies having interest and experience in the use or validation of genotoxicity assays. Contract research companies involved in predictive toxicity testing. Scientists are open for research collaboration.

Key Benefits

- Detection of genotoxic and oxidative stress-inducing properties of chemical compounds.
- Reporter systems are suitable for high throughput screening.
- Highly sensitive and specific.
- Reporter lines give reliable responses already at low toxicity concentrations.

Patent / IP Status

Two patent applications were filed in September 2010.

Applications

- Sensitive reporter systems for *in vivo* genotoxicity or oxidative stress induction.
- Screening for agents that counteract genotoxic or oxidative stress.

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