Available online at www.sciencedirect.com
ScienceDirect
Molecular Aspects of Medicine 28 (2007) 4–41
MOLECULAR ASPECTS OF MEDICINE
www.elsevier.com/locate/mam

Review

Suicide genes for cancer therapy

Daniel Portsmouth [a,b], Juraj Hlavaty [a], Matthias Renner [c,*]

[a] *Research Institute for Virology and Biomedicine, University of Veterinary Medicine, Vienna, Austria*
[b] *Christian-Doppler Laboratory for Gene Therapeutic Vector Development, Vienna, Austria*
[c] *Austrianova Biotechnology GmbH, Veterinaerplatz 1, A-1210 Vienna, Austria*

Received 15 December 2006; accepted 18 December 2006

Abstract

The principle of using suicide genes for gene directed enzyme prodrug therapy (GDEPT) of cancer has gained increasing significance during the 20 years since its inception. The astute application of suitable GDEPT systems should permit tumour ablation in the absence of off-target toxicity commonly associated with classical chemotherapy, a hypothesis which is supported by encouraging results in a multitude of pre-clinical animal models. This review provides a clear explanation of the rationale behind the GDEPT principle, outlining the advantages and limitations of different GDEPT strategies with respect to the roles of the bystander effect, the immune system and the selectivity of the activated prodrug in contributing to their therapeutic efficacy. An in-depth analysis of the most widely used suicide gene/prodrug combinations is presented, including details of the latest advances in enzyme and prodrug optimisation and results from the most recent clinical trials.

Keywords: Gene therapy; Gene directed enzyme prodrug therapy; Suicide gene; Thymidine kinase; Cytosine deaminase; Cytochrome P450; Purine nucleoside phosphorylase; Carboxypeptidase G2; Nitroreductase; Bystander effect

* Corresponding author. Tel.: +43 1 25077 2301; fax: +43 1 25077 2390.
E-mail address: renner@austrianova.com (M. Renner).

0098-2997/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mam.2006.12.001

Contents

1. Introduction

Classical chemotherapy has been established over the course of several decades as a standard treatment for cancer patients, proving successful in retarding a variety of tumour types (Chabner and Roberts, 2005). Since currently available drugs are not cancer specific, however, difficulties remain in attaining therapeutic intratumoral concentrations in the absence of systemic and off-target organ toxicity, meaning that their therapeutic index is often poor (Chatelut et al., 2003; Scripture and Figg, 2006). This is particularly the case in the treatment of solid tumours, in which poor neo-vascularisation and associated necrotic regions often render them relatively refractory to the efficient uptake of systemically delivered drugs (Jain, 2001, 2005; Munn, 2003).

Decades of cancer research, however, have provided detailed knowledge of the molecular mechanisms involved in tumorigenesis, tumour invasion, angiogenesis and metastasis, as well as those involved in tumour suppression, growth control, apoptosis and the immune response (Kufe et al., 2005). This knowledge has in turn provided targets for cancer gene therapy (Seth, 2005) and cell based therapy (CBT) (Gunzburg and Salmons, 2005; Pereboeva and Curiel, 2004), whereby exogenous genetic information is delivered to the cancer patient with the aim of effecting tumour ablation.

The majority of cancer gene therapy and CBT approaches involve strategies either to suppress the function of activated oncogenes, to restore the expression of functional tumour suppressor genes, to potentiate the anti-tumour activity of the immune system, to down-regulate angiogenesis and metastasis, or to initiate tumour self-destruction (Seth, 2005). The latter strategy can be accomplished either via the intratumoural delivery and expression of so-called ''toxic genes'', which encode proteins which cause cell death directly (Agarwal et al., 2006; Johannes and Decaudin, 2005), or by the expression of so-called ''suicide genes'', which encode enzymes which are not toxic *per se*, but which catalyze the formation of highly toxic metabolites following the application of a much less toxic prodrug. The use of suicide gene/prodrug combinations in this way is known as gene directed enzyme prodrug