Cancer Treatment Reviews 37 (2011) 618–632

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Laboratory-Clinic Interface

The emerging role of viruses in the treatment of solid tumours

M.G. Bourke [a], S. Salwa [a], K.J. Harrington [b], M.J. Kucharczyk [a], P.F. Forde [a], M. de Kruijf [a], D. Soden [a], M. Tangney [a], J.K. Collins [c], G.C. O'Sullivan [a,*]

[a] Cork Cancer Research Centre, Leslie C. Quick Jnr. Laboratory, Biosciences Institute, University College Cork, Ireland
[b] Targeted Therapy Team, The Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, United Kingdom
[c] Department of Microbiology, Food Science & Technology Building, University College Cork, Ireland

ARTICLE INFO

Article history:
Received 22 July 2010
Received in revised form 4 December 2010
Accepted 7 December 2010

Keywords:
Oncolytic virotherapy
Viral vectors for gene therapy
Viral oncolysis
Gene therapy
Immunotherapy
Multimodal therapy
Reovirus
ONYX-015
HSV-1716

ABSTRACT

There is increasing optimism for the use of non-pathogenic viruses in the treatment of many cancers. Initial interest in oncolytic virotherapy was based on the observation of an occasional clinical resolution of a lymphoma after a systemic viral infection. In many cancers, by comparison with normal tissues, the competency of the cellular anti-viral mechanism is impaired, thus creating an exploitable difference between the tumour and normal cells, as an unimpeded viral proliferation in cancer cells is eventually cytocidal. In addition to their oncolytic capability, these particular viruses may be engineered to facilitate gene delivery to tumour cells to produce therapeutic effects such as cytokine secretion and anti -tumour immune responses prior to the eventual cytolysis. There is now promising clinical experience with these viral strategies, particularly as part of multimodal studies, and already several clinical trials are in progress. The limitations of standard cancer chemotherapies, including their lack of specificity with consequent collateral toxicity and the development of cross-resistance, do not appear to apply to viral-based therapies. Furthermore, virotherapy frequently restores chemoradiosensitivity to resistant tumours and has also demonstrated efficacy against cancers that historically have a dismal prognosis. While there is cause for optimism, through continued improvements in the efficiency and safety of systemic delivery, through the emergence of alternative viral agents and through favourable clinical experiences, clinical trials as part of multimodal protocols will be necessary to define clinical utility. Significant progress has been made and this is now a major research area with an increasing annual bibliography.

Introduction

Increasing optimism exists for the use of non-pathogenic viruses, or safety-modified viral derivatives, as treatments for solid tumours. Initial interest originated from the occasionally observed clinical resolution of lymphomas in the presence of vaccination-induced viraemia or naturally occurring viral infections.[1] While multi-modality treatments based on surgical resection, in conjunction with chemotherapy and radiotherapy, have had notable success, evidence exists that the limit of what can be achieved with this approach may have been reached until the development of more effective systemic agents. Public health initiatives, the introduction of national screening programmes, refinements in operative strategy, reductions in operative mortality and advances in the detection of early cancers, rather than an increase in the efficacy of current anti-cancer agents, has resulted in the improved survival rates seen in certain solid tumour subtypes.[2–9] In addition, the recognition that many, apparently successfully treated, patients fail to remain in remission has led, in part, to the cancer stem cell hypothesis, which proposes that a subset of tumour cells, resistant to maximal treatment with current agents, survive to reconstitute the tumour or form metastases.[10] Furthermore, chemoradiotherapy lacks an ability to target cancer cells specifically, often resulting in morbidity from clinically significant cytotoxic effects on normal tissues.[9] Indeed, currently achievable dose levels are set empirically on the basis of the maximum dose that causes a known acceptable, usually 5%, incidence of serious late normal tissue damage. The objective, therefore, is to develop novel anti-cancer agents which can selectively target the cancer cells, including cancer stem cells.

Viral infection and cancer resolution – the historical perspective

For a comprehensive review of the history of oncolytic virotherapy see the report by Kelly and Russell in Molecular Therapy from 2007.[1] Throughout the 19th century, before the discovery of

* Corresponding author.
E-mail addresses: mikebourkecork@yahoo.co.uk (M.G. Bourke), slavsalwa@gmail.com (S. Salwa), kevin.harrington@icr.ac.uk (K.J. Harrington), kucharm@mcmaster.ca (M.J. Kucharczyk), patrickforde1@gmail.com (P.F. Forde), triforze@hotmail.com (M. de Kruijf), d.soden@ucc.ie (D. Soden), m.tangney@ucc.ie (M. Tangney), microbiology@ucc.ie (J.K. Collins), geraldc@iol.ie (G.C. O'Sullivan).

0305-7372/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ctrv.2010.12.003

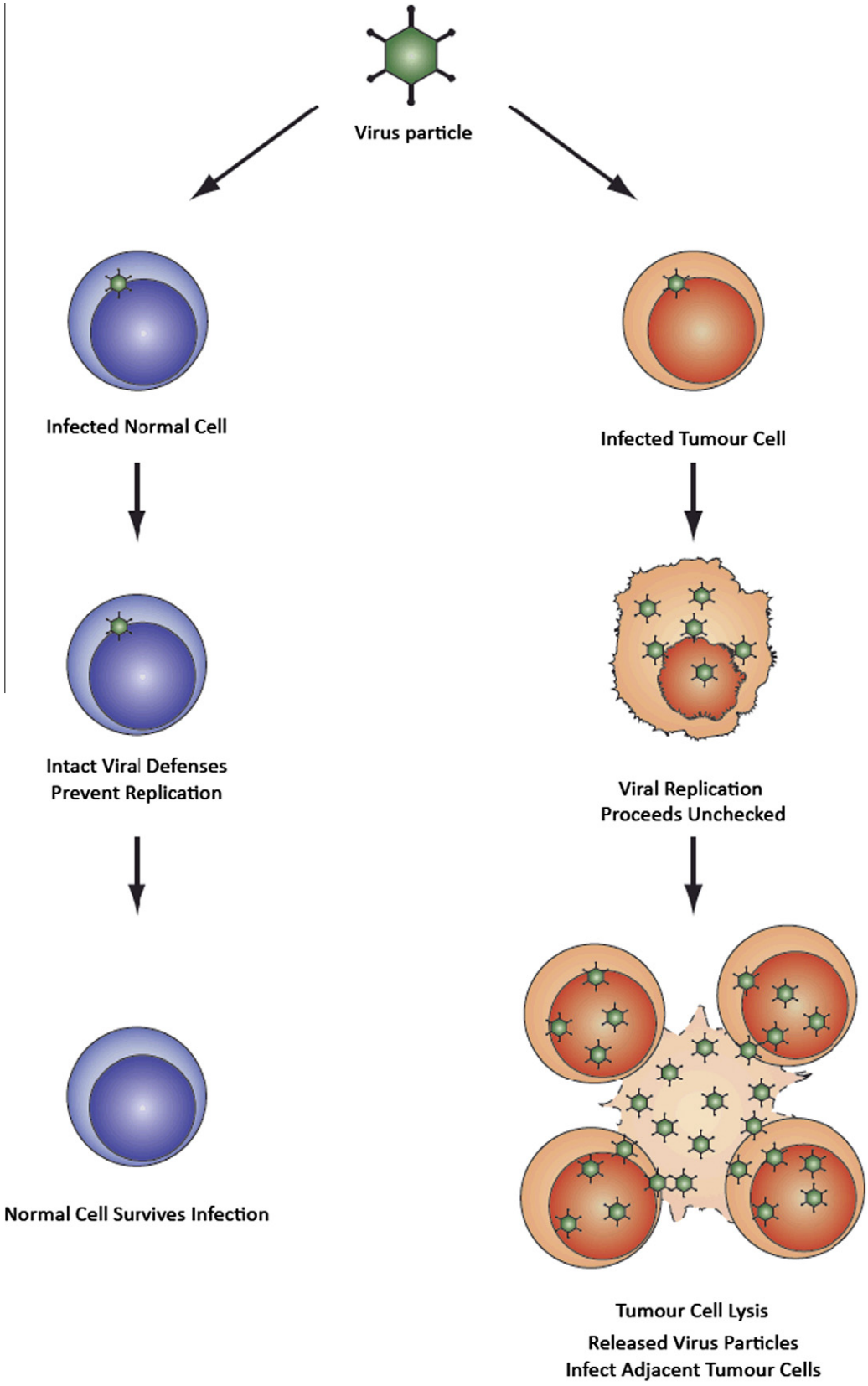

Fig. 1a. Oncolytic virotherapy. Following viral infection a normal, non-neoplastic cell is capable of evading viral infection due to its intact viral defences. By contrast, the defective viral defences associated with neoplasia result in unchecked viral replication occurring within the tumour cell, with consequent oncolysis.

viruses, there were several reports of temporary remissions of haematological malignancies associated with infective illnesses that we now know were of viral origin.[11] Based on these observations, infected body fluids of human and animal origin were used in clinical trials to transmit viral infections to patients.[12,13] Limited success was achieved with this approach, which was also hampered