Biochemical Pharmacology 90 (2014) 97–106

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Association of oncolytic adenoviruses with chemotherapies: An overview and future directions

Christian Bressy [a,b], Karim Benihoud [a,b,*]

[a] CNRS UMR 8203, Vectorologie et thérapeutiques anti-cancéreuses, Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif Cedex, France
[b] Univ Paris-Sud, 15 rue Georges Clémenceau, 91405 Orsay Cedex, France

ARTICLE INFO

Article history:
Received 10 March 2014
Accepted 5 May 2014
Available online 14 May 2014

Keywords:
CRAd
Oncolytic adenoviruses
Chemotherapeutic

ABSTRACT

Oncolytic adenoviruses have been used in different preclinical and clinical studies, showing their capacity to kill tumor cells without major adverse events. However, these studies also underline the limitations of this approach. The efficacy of oncolytic adenoviruses is hampered by their limited ability to transduce some tumor types, their lack of selectivity, and their poor dissemination within tumors. In addition, the host immune response may limit oncolytic adenovirus efficacy. Combining oncolytic adenoviruses with chemotherapeutics constitutes an appealing strategy to increase their potency. The first part of this review describes the molecular basis of oncolytic adenoviruses, their use in preclinical studies and clinical trials, their limitations, and strategies to circumvent these limitations. The second part will focus on studies combining oncolytic adenoviruses with chemotherapeutic drugs, including standard chemotherapeutic drugs, molecularly targeted drugs, and other drugs that have been combined with oncolytic adenoviruses. Finally, based on these studies, we describe future directions and general rules that could be followed to identify chemotherapeutic drugs displaying additive/synergistic effects when combined with oncolytic adenoviruses.

© 2014 Elsevier Inc. All rights reserved.

Intense interest in the use of biological agents such as viruses to treat cancer has fueled the emergence of a new class of anti-cancer agents derived from reovirus, measles virus, adenovirus (Ad), poxvirus, herpes virus and others. These new weapons, defined as oncolytic viruses, are able to replicate in tumor cells while sparing normal cells, thus eliminating the tumor with minimum side effects in patients. In order for these tools to achieve their full potential, a number of approaches are being developed to maximize the delivery, replication, and immunogenicity of the viruses [1]. This review will summarize the current knowledge of Ad-based tumor virotherapy. The characteristics of oncolytic Ad, their limitations, and current strategies to circumvent these limitations will be described, with a special emphasis on the combination of Ad-based virotherapy with chemotherapy.

1. Current status of the use of conditionally replicative adenovirus (CRAd)

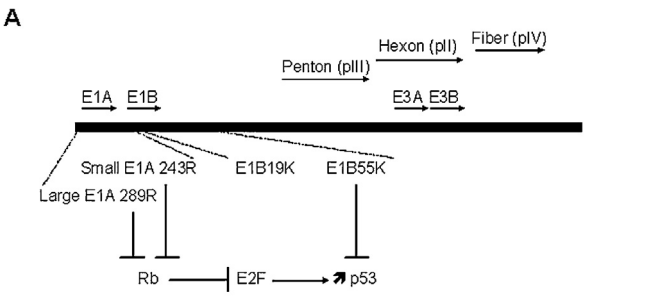
1.1. Organization of adenovirus genome

Adenoviruses constitute a large family of non-enveloped DNA virus that infect different hosts from fish to mammals. Among these viruses, human Ad serotype 5 is the best characterized in term of pathogenesis, molecular biology and protein functions. Ad entry into a target cell is followed by viral gene transcription. The first region to be transcribed, E1, is divided into E1A and E1B sub-regions [2]. E1A encodes 13S, 12S, 11S, 10S and 9S mRNA, leading to the production of 289R, 243R, 217R, 171R and 55R proteins, respectively (Fig. 1A) [3]. With the exception of the 55R protein, all of these proteins possess a CR2 domain, enabling them to interact and sequester cellular proteins of retinoblastoma family. This allows entry of the Ad-infected cell into S phase and also leads to p53 stabilization. Among the proteins encoded by E1B region,

Abbreviations: 5-FU, 5-fluorouracil; Δ24, 24 nucleotide deletion in CR2 domain of E1A region; Ad, adenovirus; AFP, α-foetoprotein; ATC, anaplastic thyroid cancer; CPA, cyclophosphamide; CPT-11, irinotecan; CR2, conserved region 2; CRAd, conditionally-replicative adenovirus; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; hTERT, human telomerase reverse transcriptase; MEKi, MEK inhibitor; MGMT, O6-methylguanine-DNA methyltransferase; MTC, mitomycine C; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; RAD001, everolimus; Rb, retinoblastoma protein; RTK, receptor tyrosine kinase; TMZ, temozolomide; TOP1, topoisomerase I; TSA, trichostatin A; VPA, valproic acid.

* Corresponding author at: CNRS UMR 8203, Vectorologie et thérapeutiques anti-cancéreuses, Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif Cedex, France. Tel.: +33 1 42 11 45 88; fax: +33 1 42 11 52 45.
E-mail address: benihoud@gustaveroussy.fr (K. Benihoud).

http://dx.doi.org/10.1016/j.bcp.2014.05.003
0006-2952/© 2014 Elsevier Inc. All rights reserved.



B

Type I CRAd

	E1A	*E1B19K*	*E1B55K*	*E3*
Onyx-015 (dl1520)	+	+	-	+
AdΔE1B55	+	+	-	-
Δ24 (del923-946)	CR2 mutation	+	+	+
dl922-947	CR2 mutation	+	+	+

Type II CRAd

	Promoter	*E1A*	*Promoter*	*E1B*	*E3*
CV787	Probasin	+	PSA	+	+
CV890	AFP	+		+	+
OBP-301 (Telomelysin)	hTERT	+		+	+

Fig. 1. CRAd engineering. (A) Viral genome map showing the localization of early (E1A, E1B, E3) and late (penton, hexon, fiber) adenoviral regions. The E1A and E1B regions encode 4 major proteins: E1A 289R, E1A 243R, E1B19K and E1B55K. E1A proteins inhibit Rb, leading to the release of E2F transcription factors and subsequent S phase entry. This cascade of events also leads to p53 stabilization. E1B55KDa inactivates p53, allowing the cell to progress in the cell cycle. E1B19KDa has anti-apoptotic properties. The black box represents the adenoviral genome and arrows indicate the direction of gene transcription. (B) Examples of different modifications made in the genome of type I or type II CRAd. These modifications correspond to viral gene mutations or deletions (type I) or to the replacement of E1 promoter by a tumor-specific promoter (type II).

E1B55 kDa has the capacity to inhibit p53 protein, unleashing G1/S transition; whereas E1B19 kDa possesses anti-apoptotic activity (Fig. 1A). Proteins produced by E2, E3 and E4 regions are involved respectively in Ad replication, the control of the host immune response, and the shutting off of the nuclear export of cellular transcripts. There is only one late transcription unit that allows production of the Ad structural proteins hexon, fiber and penton base, which are essential components of the viral capsid. Following their production, virions are released through a yet poorly defined mechanism that includes autophagy and apoptosis [2].

More than 20 years ago, knowledge of the fine regulation of Ad5 biology led not only to the development of non-replicative Ad with deletions of the E1 (and E3) regions, but also to the design of conditionally replicative Ad (CRAd) [4]. Replication-defective Ads are used for gene therapy and vaccination, while CRAd are able to destroy cancer cells because of their oncolytic activity.

1.2. Definition and subtypes

CRAd have been designed to infect, replicate and kill cancer cells while sparing normal cells. Following infection and replication in tumor cells, oncolytic viruses kill the cells, releasing virions for subsequent cycles of amplification. To achieve replication only into tumor cells, two kinds of genetic modifications have been made, leading to 2 subclasses of CRAd [5].

Type I CRAd are characterized by mutations or deletions in the E1 region of the genome, interfering with the inactivation of cell cycle regulators such as p53 and retinoblastoma protein (Rb) (Fig. 1A). As a consequence, type I CRAds replicate in actively dividing tumor cells. For example, Onyx-015, also known as dl1520, which is unable to express the E1B-55 kDa protein, is unable to inactivate p53 and avoid p53-induced cell cycle arrest. Several studies attributed the molecular basis of Onyx-015 selectivity to the lack of expression of p53 or one of genes involved in p53 pathway. However, O'Shea et al. showed that late viral RNA export, rather than p53 inactivation, determines Onyx-015 virus selectivity [6]. Other type I CRAds with deletions in the E1A region are unable to bind Rb and trigger S phase entry. For example, dl922-947 [7] and Δ24 [8] contain a 24 nucleotide deletion in CR2 domain of E1A region, abrogating E1A–Rb interaction. As a result, these viruses replicate mainly in tumor cells (Fig. 1B).

Another way to restrict adenoviral replication to tumor cells is to regulate the transcription of viral genes required for viral replication. In type II CRAds, the genome is placed under the control of a tumor-specific promoter (Fig. 1B). Those promoters were derived from genes known to be preferentially expressed in some tumors compared to normal tissue (*e.g.*, telomerase or cyclooxygenase II); or that are overexpressed in tumors (*e.g.*, prostate specific antigen, PSA or α-foetoprotein, AFP) compared to normal tissues [5].

1.3. Characterization of conditionally replicative adenovirus in preclinical models and clinical trials

CRAds are characterized *in vitro* in different tumor models of human origin as well as in normal cells. This step helps both to define CRAd replication potential in different tumors and to assess their low replication in normal cells. CRAd *in vivo* efficacy is analyzed in different models of human tumor cells xenografted on nude mice. CRAd may be administered directly into the tumor, injected systemically, or in the case of ovarian carcinoma metastasis model, injected intra-peritoneally. Whatever the mode of administration, CRAd efficacy is evaluated by monitoring tumor growth and mouse survival and the results are correlated to viral gene expression and virion production. Because intravenously injected Ad has a strong liver tropism, CRAd replication in normal cells is evaluated by measuring different parameters of liver toxicity [5]. It should be emphasized that *in vivo* models based on nude mice xenografted with human tumors cannot provide information regarding the influence of the host's specific immune responses on CRAd efficacy. In some studies, murine cells capable of supporting CRAd replication were grown in syngenic murine models [9]. More recently, a Syrian hamster model permissive for Ad virus replication was proposed to measure CRAd efficacy and toxicity [10].

CRAds have been used as single agents in several phase I and II clinical trials. The vast majority of these studies were performed with the type I CRAd Onyx-015. In a phase I study of patients with refractory head and neck cancers, Onyx-015 was injected intratumorally [11]. There was no dose-limiting toxicity reported and the virus was well tolerated, with flu-like symptoms reported as the main toxicity. Interestingly, viral replication was observed in some patients [11]. In another study of patients with refractory head and neck cancers, a comparable safety profile was observed and partial to complete responses were obtained in about 10% of patients [12]. Intravenously administered Onyx-015 was also tested in a phase II clinical trial of patients with metastatic colorectal cancer refractory to chemotherapy. Patients in this study displayed some flu-like symptoms and viral DNA was detected in serum at some distance from the virus injection, suggesting effective viral replication. Interestingly, 7 patients out of 18 presented as having stable disease after 2 months of treatment [13]. Other clinical trials have been performed with type II CRAds.

Download English Version:

https://daneshyari.com/en/article/5823548

Download Persian Version:

https://daneshyari.com/article/5823548

Daneshyari.com