Fundamental Biomedical Technologies

Aleš Prokop *Editor*

Intracellular Delivery

Fundamentals and Applications

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Intracellular Delivery

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Editorial and Introduction

Intracellular delivery: Fundamentals and applications A special volume of the series – Fundamental Biological Technologies (http://www.springer.com/series/7045), Professor M. Ferrari, Editor.

This book features a special subsection of Nanomedicine, an application of nanotechnology to achieve breakthroughs in healthcare. It exploits the improved and often novel physical, chemical and biological properties of materials only existent at the nanometer scale. As a consequence of small scale, nanosystems in most cases are efficiently uptaken by cells and appear to act at the intracellular level. Nanotechnology has the potential to improve diagnosis, treatment and follow-up of diseases, and includes targeted drug delivery and regenerative medicine; it creates new tools and methods that impact significantly existing conservative practices. This book more specifically targets nanotechnology in the area of drug delivery, i.e. the application of various nanoparticulates based on natural or synthetic, organic or inorgarnic materials as drug carriers, first of all to deliver drugs inside cells.

During the last decade, intracellular drug delivery has become an emerging area of research in the medical and pharmaceutical field. Many therapeutic agents can be delivered to a particular compartment of a cell to achieve better activity. It is very prolific field as it appears that the pace of discovery of intracellular drugs (to cellular or organ compartments) is proceeding faster than conventional ones. The lipidic nature of biological membranes is the major obstacle to the intracellular delivery of macromolecular and ionic drugs. Additionally, after endocytosis, the lysosome, the major degradation compartment, needs to be avoided for better activity. Various carriers have been investigated for efficient intracellular delivery, either by direct entry to cytoplasm or by escaping the endosomal compartment. These include cell penetrating peptides, and carrier systems such as liposomes, cationic lipids and polymers, polymeric nanoparticles, etc. Various properties of these carriers, including size, surface charge, composition and the presence of cell specific ligands, alter their efficacy and specificity towards particular cells. This book summarizes various aspects of targeted intracellular delivery of therapeutics including pathways, mechanisms, and approaches. Several case studies featuring a high success at an industrial scale are reviewed.

This volume is a collection of authoritative reviews. We first cover fundamental routes of nanodelivery devices cellular uptake, types of delivery devices, particularly in terms of localized cellular delivery, both for small drug molecules, macromolecular drugs and genes; all at academic and applied levels. Following is dedicated to

enhancing delivery via special targeting motifs. Second, we introduce different types of intracellular nanodelivery devices (chemistry, although the coverage is far from complete) and ways of producing these different devices. Third, we put special emphasis on particular disease states and on other biomedical applications. Diagnostic and sensing is also included.

This is a very pregnant topic which will stir great interest. Intracellular delivery enables much more efficient drug delivery since the impact (on different organelles and sites) is intracellular as the drug is not supplied externally. There is a great potential for targeted delivery to certain cells or even to certain intracellular compartments with improved localized delivery and efficacy.

The Part I of this Volume deals with nanoparticle uptake and targeting and functionalization tools available to facilitate and enhance their internalization. The passive uptake and entry of nanoparticles into the subcellular space and its organelles could be enhanced with a targeting motifs via an active entry. Targeting, localized and intracellular delivery present still a key challenge to effective delivery. To establish an effective fight against diseases, we have to have the ability to selectively attack specific cells, while saving the normal tissue from excessive burdens of drug toxicity. However, because many drugs are designed to simply kill specified cells, in a semi-specific fashion, the distribution of drugs in healthy organs or tissues is especially undesirable due to the potential for severe side effects. Consequently, systemic application of these drugs often causes severe side effects in other tissues (e.g. bone marrow suppression, cardiomyopathy, neurotoxicity), which greatly limits the maximal allowable dose of the drug. In addition, rapid elimination and widespread distribution into non-targeted organs and tissues requires the administration of a drug (in a suitable carrier) in large quantities, which is often not economical and sometimes complicated due to non-specific toxicity. This vicious cycle of large doses and the concurrent toxicity is a major limitation of many current therapies. In cancer treatment, in many instances, it has been observed that the patient succumbs to the ill effects of the drug toxicity far earlier than the tumor burden (for example). All above calls for focused attention to mechanisms of entry and targeting and studies how to avoid reticulo-endothelial system (RES) capture (sometimes such affinity is employed to our advantage – see lymphatic targeting). Futhermore, while the nanoparticles entry is always associated with particle repulsion, exocytosis is also covered, although it deserves greater atention as many carriers/drugs could be eliminated from inside the cell even they enter the intracellular millieau. Some special peptide-based targeting mechanisms are covered at the end of this part. Such peptide motifs are often employed to facilitate proper cellular entry once associated with nanocarriers.

For a single, even very sizable book, some important topics unfortunately are not covered here, such as dual targeting, combination therapy, multivalency, transport across the blood-brain barrier and some aspects of toxicity. Other neglected area is that of chemical vectors for non-viral gene delivery that mimic some viral functions and ultrasound-enhanced uptake.

Nanoparticle preparation is the subject of Part II of the Volume. Although not all possible chemistries are being covered, still the available information presents this important area in good details. Some chapters deal with employment of natural polymers, others with synthetic or semi-synthetic ones. Inorganic systems are also described. A special emphasis is on the synthesis of magnetic nanoparticles and metalic-based, biosynthetically synthesized nanoparticles, which are present in a bionanocomposite (enmesshed) form with microroganisms. This Part is closed by articles on processing and scale-up, the very significant consideration often limiting the commerical application in general. Some special formulations are also covered in Part III of this Volume (e.g., inorganic – calcium phosphate nanoparticles).

The Part III deals with specific medicinal applications. In doing so, we were unable to cover all related topics because of Volume space limitation. Among those covered, some are quite new, such as new imaging modes and stem cell tracking. In our opinion, a special attention should be paid to coverage of bioinformatics (and systems biology) as an important tool, which is going to shape the whole medicine in a near future.

We strongly believe that the intracellular delivery/therapy is a very pregnant topic, which will stir great interest. Intracellular delivery enables much more efficient drug delivery since the impact (on different organelles and sites) is intracellular as the drug is not supplied externally within the blood stream.

As was said, the topic of intracellular delivery is so broad that not all aspects could be covered. Great emphasis is on the state-of-the art topics. Unfortunately, we could not avoid some overlap in covering individual topics. Thus, while there is a considerable attention (and some overlap) devoted to entry mechanisms and targeting, we would like to emphasize its importance towards the rational nanocarrier design.

The Editor would like to profoundly thank all Contributors to this Volume for their cooperation and enthusiasm. It is also noted that the authorship coverage is truly international, in spite of apparent “concentration” of nanoactivity in USA.

Aleš Prokop, Editor and
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Part I
Mechanisms of Uptake and Targeting

Mass Transport via Cellular Barriers and Endocytosis

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Abstract Mass transport within body compartments and across biological barriers negatively impacts drug delivery but also presents opportunities to optimally design drug carriers that benefit from novel differentials presented in pathological tissue. As an example, cancer presents unique alterations in vascular permeability, osmotic pressure, cellular zip-codes, and numerous other physical parameters that can be used to achieve preferential accumulation of imaging and therapeutic agents at the cancer lesion. This chapter describes the journey of drug delivery from the site of administration to the appropriate subcellular compartment within the target cell. Design parameters for optimal fabrication of nanoparticle-based carriers, including size, shape, elemental composition, surface staging, and hierarchical ordering of multi-particle complexes are presented. The overall objective of this chapter is to enhance our understanding of mass transport in order to facilitate the development of carriers for therapy and diagnostics of various pathological conditions.

Keywords Mass transport • Cellular targeting • Drug delivery • Endocytosis • Nanoparticle • Cellular zip codes • Nanoparticle carriers • Multi-particle complexes • Nanoparticle parameter tuning • Particle delivery • Intracellular transportation • Intracellular delivery • Paracellular transport

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Abbreviations

RES	reticulo-endothelial system
SLC	solute carriers
OATP	organic anion transporting polypeptides
PEPT-1 and SLC15A1	Oligopeptide Transporter 1
MCT1 and SLC16A1	mono-carboxylic acid transporters
gp60	cell surface glycoprotein receptor
ECM	extracellular matrix
VEGF	vascular endothelial growth factor
EPR	enhanced permeability and retention
TGF-β1	transforming growth factor beta one
CendR	C end Rule
iRGD	internalizing Arginine-Glycine-Aspartic acid
HGC	hydrophobically modified glycol chitosan
LAMP-1	Lysosomal-associated membrane protein 1
SWNT	single walled carbon nanotubes
I-CAM	intercellular adhesion molecule one
GRP78	78 kDa glucose-regulated protein
DTPA	Diethylene triamine pentaacetic acid
EC20	Endocyte 20
EC17	Endocyte 17
EC145	Endocyte 145
LHRH	leutinizing hormone releasing hormone
PLGA	Poly(lactide-co-glycolide)
LDL	low density lipoproteins
PSMA	Prostate Specific Membrane Antigen
PEG	polyethylene glycol
siRNA	small interfering RNA
gp120	HIV-1_{BAL} envelop glycoprotein
PK2	doxorubicin carrying polymer conjugated to galactose
ADEPT	antibody directed enzyme prodrug therapy
NV	nanovehicular
QD	quantum dots
PEI	polyethylenimine
NLS	nuclear localization signal
HIV-TAT	human immunodeficiency virus Trans-Activator of Transcription
ER	endoplasmic reticulum
V+ATPase	vacuolar proton transporter
EMMA	Endosomolysis by Masking of a Membrane-Active Agent
RER	rough endoplasmic reticulum
SER	smooth endoplasmic reticulum
PDI	protein disulfide isomerase
BiP	binding immunoglobulin protein