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1. Introduction

Pharmaceutical nanoparticles were first described in 1970s, and the term “nanotechnology” is now commonly used to refer to the fabrication of new materials with nanoscale dimensions between 1 and 100 nm (Thrall 2004). Several types of nanometer scale systems such as nanoparticles, nanospheres, nanotubes, nanogels and molecular conjugates are being investigated (Lemieux et al. 2000; Liu et al. 2007; Ravi et al. 2004). The field of nanomedicine aims to use the properties and physical characteristics of nanomaterials which have been extensively investigated as novel intravascular or cellular probes for both diagnostic (imaging) and therapeutic purposes (drug/gene delivery). The sub-micron size of nanoparticle delivery systems confers distinct advantages as compared to large sized systems including targeted delivery, higher and deeper tissue penetrability, greater cellular uptake and greater ability to cross the blood-brain barrier (Kreuter et al. 1995; Vinogradov et al. 2002; Vogt et al. 2006). Therapeutic transgene(s) encoded by plasmid or chemically modified DNA can be dissolved, entrapped, chemically conjugated, encapsulated or adsorbed to the surface of nanoparticles. There are, broadly, two main types of nanosized particles with different inner structures: A. Nanoparticle/Nanosphere: Matrix composed of entangled oligomer or polymer units; and B. Nanocapsule: Reservoir consisting of a hydrophobic core surrounded by a polymer wall. Lipids can also be used to generate liposomes or micelles (discussed in detail later). These nanodevices can confer protection to the DNA against a variety of degradative and destabilizing factors, and enhance delivery efficiency to the cells while minimizing the toxic effects. Nanoparticles are expected to play a critical role in the innovation and development of future cancer treatment modalities. Recent research has developed functional nanoparticles that are covalently linked to biological molecules such as peptides, proteins, nucleic acids, or small-molecule ligands (Alivisatos 2004; Chan et al. 2002; Michalet et al. 2005). Medical applications have also appeared, such as the use of superparamagnetic iron oxide nanoparticles as a contrast agent in the detection of lymph node prostate cancer (Harisinghani et al. 2003) and the use of polymeric nanoparticles for targeted gene delivery to tumor vasculatures (Hood et al. 2002). Target-specific drug/gene delivery and early diagnosis is currently a high priority R&D area, and one in which nanomedicine will inevitably make critical contributions. Current modalities of diagnosis and treatment of various diseases, especially cancer, have major limitations such as poor sensitivity or
specificity and high drug toxicities respectively. The success of nanoparticle delivery systems will ultimately depend on the ability to efficiently deliver the gene of interest and express a therapeutic gene(s) in tumor cells in a targeted manner in order to mitigate toxicity. This chapter examines current existing nanoparticle-based gene therapy approaches to cancer treatment, and assesses their therapeutic utility.

2. Nanobased cancer treatment strategies

Most neoplasms are derived from multiple mutations and rarely can be controlled through the targeting of a single mutation. The efficacy of gene therapy in tumor treatment will undoubtedly rely upon the simultaneous targeting of multiple cellular processes or the ability to invoke various antitumor responses. Current clinical trials in cancer exploit a variety of different treatment approaches. Tumor suppressor modalities compensate for a genetic mutation via gene transfer or replacement of an altered tumor suppressor gene (e.g. p53, BRCA1). Molecular chemotherapy, involves the transfer of a suicide gene (e.g. Herpes Simplex Virus-thymidine kinase [HSV-tk], CD40L) targeted to specific tissues by extracellular tumor/tissue targeting strategies, and/or via tissue-specific expression. The delivered gene then makes the cell susceptible to a prodrug (e.g. gancyclovir, 5-FC) making tumor-specific expression critical. Tumor immunotherapy involves the gene transfer of cytokines (e.g. IL-2, IL-12) that impart antitumor immunomodulatory properties. Oncofactor inhibition strategies such as growth factor inhibition and oncogene inhibition (e.g. erb-B2 silencing) aim to impede tumor progression by inhibiting key growth factors. Anti-angiogenesis therapy seeks to destroy the vasculature supplying the tumor in the hopes of starving it of essential nutrients to diminish or prevent its progression. Multi Drug Resistance associated genes strategies, involve knocking down gene associated with or conferring MDR, such as PRF-4 and survivin to improve chemosensitivity. We will examine in detail each of these strategies.

2.1 Tumor suppressor gene therapy

As a critical player in cancer onset, p53 has come to the forefront of oncological research and is now recognized to be the single most frequently inactivated gene in human cancers (Ning et al. 2011; Olivier et al. 2002; Olivier et al. 2010). The p53 gene enforces a variety of anticancer functions by encouraging cells to arrest or die in the face of DNA damage, hypoxia, oxidative stress, excessive mitogenic stimuli or denuded telomers. In addition, the protein influences several biological functions such as involvement in cell cycle regulation, programmed cell death, senescence, differentiation and development, transcription, DNA replication, DNA repair and maintenance of genomic stability. Thus, it’s not surprising that p53 is regarded as the “Guardian of the Genome” in preventing human neoplasia (Lane 1992). P53 protein has emerged as a key tumor suppressor protein in cellular stress response pathways. The p53 gene, mapped to chromosome 17p13.1, consists of 11 exons spanning over 20 kb of DNA encoding a 393 amino acid and 53 kDa nuclear protein. Its structure consists of an acidic N-terminus with a transactivation domain, a hydrophobic central DNA-binding core and a basic C-terminus with regulatory and oligomerization domains (Hainaut and Vahakangas 1997). Although greater than 90% of the isolated mutations in this gene have been localized to the DNA binding site of p53, coded by exons 5 to 8; some mutations have also been reported outside the evolutionary conserved regions (Hainaut and Hollstein).


This book focuses on recent advancement of gene delivery systems research. With the multidisciplinary contribution in gene delivery, the book covers several aspects in the gene therapy development: various gene delivery systems, methods to enhance delivery, materials with modification and multifunction for the tumor or tissue targeting. This book will help molecular biologists gain a basic knowledge of gene delivery vehicles, while drug delivery scientist will better understand DNA, molecular biology, and DNA manipulation.

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