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Polymer genomics: An insight into pharmacology and toxicology of nanomedicines☆

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Abstract

Synthetic polymers and nanomaterials display selective phenotypic effects in cells and in the body signal transduction mechanisms involved in inflammation, differentiation, proliferation, and apoptosis. When physically mixed or covalently conjugated with cytotoxic agents, bacterial DNA or antigens, polymers can drastically alter specific genetically controlled responses to these agents. These effects, in part, result from cooperative interactions of polymers and nanomaterials with plasma cell membranes and trafficking of polymers and nanomaterials to intracellular organelles. Cells and whole organism responses to these materials can be phenotype or genotype dependent. In selected cases, polymer agents can bypass limitations to biological responses imposed by the genotype, for example, phenotypic correction of immune response by polyelectrolytes. Overall, these effects are relatively benign as they do not result in cytotoxicity or major toxicities in the body. Collectively, however, these studies support the need for assessing pharmacogenomic effects of polymer materials to maximize clinical outcomes and understand the pharmacological and toxicological effects of polymer formulations of biological agents, i.e. *polymer genomics*.

Keywords: Artificial vaccines; DNA microarray; Drug resistance; Signal transduction; Phenotype

Contents

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✠ In memory of Academician Victor Alexandrovich Kabanov (1934–2006).

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1. Introduction

This work focuses on the pharmacogenomic effects of synthetic polymers and nanomaterials used in delivery of drugs, genes, and antigens. This new and relatively unexplored field is called "*polymer genomics*" [1]. Pharmacogenomics has emerged as an important field at the interface of pharmaceutics and genetics, which studies how an individual's genetic inheritance affects the body's response to drugs [2]. It holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Of equal importance are studies of cellular responses to drugs, particularly, in cancer chemotherapy and other areas where biological agents can select for genetic mutations that result in acquired resistance to these agents [3]. Such studies are employing methods of functional genomics, proteomics and bioinformatics to characterize cellular responses to drugs. Based on these foundations polymer genomics investigates how polymers and nanomaterials alter cell and whole body responses to biological agents. Rapid development of nanotechnology has recently brought considerable attention to the problem of toxicity of nanomaterials [4]. Because of the enormous promise that nanotechnology holds for society the concern about the safety of nanomaterials has also become very profound. Novel engineered nanomaterials have unique physicochemical properties including small size, shape, high surface area, surface activity and chemical composition. Due to these properties these nanomaterials can exhibit toxic effects and may represent a considerable hazard. The toxicogenomic approach is now applied to nanotechnology to understand the origins of toxicity of nanomaterials and develop safe nanomaterials and processes.

Notably, the problem of toxicity of nanoscale materials is not new and was encountered by drug delivery researchers several decades ago in the context of toxicity of water-soluble synthetic polymers, liposomes, nanoparticles and other nanoscale objects [5–7]. The problem has been addressed in many cases by the development of biodegradable polymers, optimization of polymer chemical composition, surface coating of liposomes and nanoparticles and other approaches. Several, nanoscale drugs ("*nanomedicines*"), such as liposomal Doxorubicin, Doxil [8] or albumin-bound Paclitaxel, Abraxane [9] have been used in clinic. Others, such as Doxorubicin incorporated in polymer micelles, SP1049C [10,11] and NK911 [12] are in clinical trials. Clearly, some of the approaches developed in these earlier studies can and will be extended to improve safety of novel engineered nanomaterials, thus addressing major obstacles to their use in a human body. However, even safe polymers and nanomaterials developed for human use may affect the responses to biological agents in the body and these interactions are currently not well understood.

The relevance and urgency of such consideration in pharmaceutics has become most obvious because of the tremendous growth of work using polymer-based drug and gene delivery systems. The central paradigm of polymer-based drug delivery systems considers polymers used in these formulations as *biologically inert* excipients that protect biological agents from degradation, prolong their exposure to tissues, and enhance transport of biological agents into cells. However, such a view is undergoing major revision due to growing evidence that selected synthetic polymers, when combined with the biological agents (low molecular mass drugs, DNA or antigens), can alter genetically controlled cellular responses to these agents [1,13–15]. This paper provides an overview of such studies. First, we consider polymers and nanomaterials that are currently used or developed for delivery of biologically active agents, and highlight