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Pulmonary administration of therapeutic proteins using an immunoglobulin transport pathway ☆

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Abstract

We have applied a "physiologic" approach to the pulmonary delivery of therapeutic proteins, utilizing an immunoglobulin (antibody) transport pathway recently shown to be present predominantly in the conducting airways of the human respiratory tract. Therapeutic proteins are fused to the Fc-domain of an IgG1, allowing them to bind with high affinity to the antibody transport receptor, FcRn. Liquid aerosols are administered into the lung using normal breathing maneuvers and efficient delivery of several different Fc-fusion proteins has been achieved with retention of biological activity and an increase in circulating half-life. A new paradigm for the pulmonary delivery of therapeutic proteins and a fundamental advance in the construction of Fc-fusion proteins for this purpose will be described.

Keywords: FcRn; Transepithelial transport; Erythropoietin; Interferon alpha; Interferon beta; Follicle stimulating hormone; Aerosol; Fc-fusion protein; Neonatal Fc receptor; Lung

Contents

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1. Introduction

1.1. The lung for protein drug delivery

The use of the lung as an alternative route of delivery for protein and peptide drugs has been explored for several decades [1–4], with the most extensive experience and success in man being with insulin, a relatively small protein [5]. While studies in animals with several larger therapeutic proteins have demonstrated satisfactory bioavailability after pulmonary delivery [6–8], the human lung has remained relatively impenetrable to these molecules despite significant efforts to design new formulations and devices to overcome the barriers to effective systemic delivery [9,10].

1.2. Immunoglobulin transport and protection

The study of immunoglobulin (IgG) transport has its roots in work conducted by Brambell and others aimed at understanding the passive transmission of immunity (i.e. antibodies) from mother to her young during the perinatal period of life [11,12]. This early work forms the basis for our understanding of the transport processes that are central to the pulmonary delivery technology outlined in this review. Antibody transport in these seemingly disparate settings is mediated by the same neonatal Fc receptor, FcRn, so named because of its original isolation from the intestine of neonatal rats [13,14]. The details of IgG transport are outlined below.

IgG is taken into epithelial cells from the surrounding milieu by pinocytosis [15–17]. A coated vesicle is formed by invagination of the plasma membrane, entrapping IgG along with other solutes in the lumenal fluids. Some binding of IgG to the transport receptor, FcRn, may occur at the plasma membrane [18,19], but it is more likely that most of the binding takes place intracellularly because the majority of FcRn appears to be localized within acidic endosomal vesicles within the cell; little FcRn being detectable at the cell surface [20]. The transport vesicles containing IgG bound to FcRn do not fuse with the degradative lysosomes, but rather pass through the epithelial cell in the apical to basolateral direction with eventual release of intact IgG to the interstitial space. This transport process known as transcytosis, is essentially unidirectional in a physiological setting, being driven by the strong pH dependence of the binding to FcRn and the pH gradient between the lumenal and serosal exposures of the epithelial cells. IgG binds tightly to FcRn at the slightly acidic pH of 6.0–6.5 found in the fluids bathing the epithelial cells as well as at the pH in the acidic vesicles containing FcRn [21,22]. There is no binding of IgG to FcRn at the neutral to slightly alkaline pH found in the interstitial space and this enables the release of IgG from FcRn after fusion of the transport vesicles with the plasma membrane at the basolateral side of the epithelial cells. Passage of IgG into the circulation is most likely primarily paracellular because of the absence of tight junctions between endothelial cells [2].

IgG is exceptionally stable in the bloodstream having a half-life of approximately 21 days in humans. In 1964, Brambell proposed that the same receptor protein that transported IgG through epithelial cells served also to protect them from degradation in the bloodstream [23]. We know now that FcRn is indeed the receptor involved in protecting circulating IgG from degradation in addition to its transport function [24,25]. IgG is taken up into endothelial cells lining the vasculature by a pincytotic process similar to that found in the epithelial cells, but unlike in the epithelial cell, IgG does not undergo transcytosis in the endothelial cell.