simple passive diffusion. In addition, receptor binding of small molecules is important for their PD effect but the fraction bound to the receptors rarely plays a role in their PK. Surprisingly, some large molecule drugs also bind to circulating plasma proteins, which may influence their PK and PD in similar ways as for small molecule drugs. Unlike small synthetic molecules for which different metabolic pathways exist in different species, the clearance mechanism for peptides and proteins is generally conserved across mammalian species. As a result, the PK of many protein drugs can be scaled mathematically between species. In contrast to most small molecule drugs, large molecule therapeutics may be immunogenic and circulating antibodies can influence their PK and PD.

2. CLEARANCE MECHANISMS OF PROTEIN THERAPEUTICS

It is commonly accepted that peptide and protein drugs are metabolized through identical catabolic pathways as endogenous and dietary proteins. Generally, proteins are broken down into amino acid fragments that can be re-utilized in the synthesis of endogenous proteins. Although history has shown that proteins can be powerful and potentially toxic compounds, their end products of metabolism are not considered to be a safety issue. This is in contrast with small organic synthetic drug molecules from which potentially toxic metabolites can be formed. The study of the metabolism of protein drugs is also very complicated because of the great number of fragments that can be produced. The mechanisms for elimination of peptides and proteins are outlined in Table 1.

2.1. Proteolysis

Most, if not all, proteins are catabolized by proteolysis. Proteolytic enzymes are not only widespread throughout the body, they are also ubiquitous in nature, and therefore the potential number of catabolism sites on any protein is very large (1–3). It has been shown for interferon-α (IFN-α) that truncated forms are present in the circulation after dosing of rhesus monkeys with rIFN-α. The rate and extent of production of these metabolites may be dependent on the route of administration. This, and the cross-reactivity of these degraded forms in the ELISA may be responsible for the observation of a bioavailability of more than 100% after subcutaneous administration of rIFN-α (4). Proteolytic activity in tissue may be responsible for the loss of protein after subcutaneous administration.

2.2. Renal Excretion and Metabolism

Metabolism studies of peptide and protein drugs were performed to identify the organs responsible for metabolism (and/or excretion), and their relative contribution to the total elimination clearance. The importance of the

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