Delivery Systems for Immunomodulatory Proteins and Peptides

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Summary

Polypeptide and protein immunomodulators are subject to absorption, biodistribution, metabolism and degradation at sites and rates which may not permit effective interactions with components of the immune system. Drug carrier technology can overcome some of these obstacles. Because of the lipid and particulate nature of liposomes, increased delivery of immunomodulators to lymphatics, lymph nodes, lymphatic organs and concentrations of macrophages is possible when an immunomodulator is associated with a liposome. Interleukin-2 (IL-2)
1. Overview

1.1 Targeting of Immunomodulatory Peptides and Proteins to the Immune System

The immune system is diffusely located throughout the body as well as being concentrated in specialised lymphatic organs including lymph nodes, bronchial-associated lymphoid tissue, gut-associated lymphoid tissue, thymus and spleen. Protein and polypeptide immunomodulators may act on lymphoid and/or accessory cells, including macrophages. Since immunomodulatory proteins are usually digested and degraded into inactive fragments after oral administration, parenteral strategies have been generally necessary for in vivo effectiveness. However, parenteral administration of some protein and peptide immunomodulators has been relatively ineffective because biodistribution after subcutaneous and/or intravenous injection does not permit effective interaction with cells of the immune system. Numerous delivery systems have been used with immunomodulators in order to facilitate more effective interaction with various components of the immune system, ameliorate toxicity, and to provide more convenient schedules and routes of administration. This review will detail some specific examples where delivery systems of immunomodulatory peptides and proteins have enhanced the effectiveness of peptide and protein immunomodulators. Advantages of delivery systems for peptides and proteins are listed in table I; potential problems inherent in use of some of these approaches are listed in table II.

1.2 Drug Delivery Systems

Effective immune responses may involve many steps, including:
- delivery of an antigen to a collection of phagocytic cells
- antigen binding and internalisation in macrophages or dendritic cells
- processing and presentation of peptide fragments by antigen-presenting cells to T cells in

Polypeptides can also enhance the interaction of an immunomodulator with the immune system via increased immunostimulation; this can provide a means to enhance oral delivery and to achieve depot effects. Polysaccharide microspheres have been shown to be effective biodegradable carriers of immunomodulators.

Finally, genetically engineered bacteria, viruses and mammalian cells may function as delivery systems for immunomodulatory peptides and proteins. Attenuated Salmonella strains can deliver immunomodulators to the gut-associated lymphoid tissue, liver and spleen. In mouse experiments using tumour cells producing granulocyte-macrophage colony-stimulating factor (GM-CSF), irradiated tumour preparations produced GM-CSF and were capable of eliciting effective cell-mediated immune responses, including destruction and elimination of tumour as well as resistance to tumour challenge (i.e. memory response). A wide variety of immunomodulators have been tested using this strategy; IL-2 and GM-CSF are among the most potent inducers of both cell-mediated effector and memory responses.

In summary, use of delivery systems can significantly enhance the immunomodulatory potential of polypeptides and proteins.