Chapter 25

A New Approach to Vaccine Adjuvants

Immunopotentiation by Intracellular T-Helper-Like Signals Transmitted by Loxoribine

Michael G. Goodman

1. INTRODUCTION

1.1. Discovery of Loxoribine and Its Analogues

Vaccination with innocuous antigens derived from pathogenic microorganisms is designed to provide protection against the significant morbidity and mortality associated with diseases caused by these pathogens. Vaccination is most important precisely in those patients who are most likely to have difficulty mounting an adequate immune response either to the intact pathogen or to the vaccinating antigen, that is, those patients with acquired permanent or temporary immunodeficiencies. These patients manifest defects in one or more cell lineages that can involve deficient antigen processing, antigen presentation in the context of appropriate major histocompatibility antigen (MHC) molecules, transmembrane signal transduction, signal transmission, cytokine generation, cytokine receptors, and so forth. Among the striking advantages of the compounds discussed in this chapter is the ability to overcome or ameliorate many obstacles to effective immune responses against the epitopes of pathogenic microorganisms. This property appears to be unique to the 7,8-disubstituted guanine nucleosides.

The C8-substituted guanine ribonucleosides were first discovered while studying the role of cyclic GMP (cGMP) in B-cell activation (Goodman and Weigle, 1981, 1982a,b). At the time, there was considerable controversy in the literature concerning the role of cGMP in B-cell activation (Watson et al., 1973; Watson, 1975; Coffey et al., 1977; Diamantstein and Ulmer, 1975; Weinstein et al., 1974, 1975; Wedner et al., 1975; Burleson...
One of the central issues of disagreement was the ability of exogenous cGMP to induce mitogenesis in cultured B cells. However, different investigators used different cGMP analogues, some of which (e.g., dibutyryl cGMP and 8Br-cGMP) were designed to be highly lipophilic to increase the likelihood that the cyclic phosphate would cross the plasma membrane. We discovered that the manner of substitution of various cGMP analogues was relevant to more than the ability of the molecule to cross the plasma membrane. Thus, undervatized cGMP as well as dibutyryl cGMP were not effective B-cell stimulants. However, 8-bromo-cGMP was consistently effective as a B-cell activator. In subsequent experiments the cyclic phosphate nature of the molecule was shown to be irrelevant to its stimulatory capacity, such that 8-bromoguanylic acid is more active than 8-bromo-cGMP, and more potent by approximately one order of magnitude. 8-Bromoguanosine, lacking the 5' phosphate group, is more active still. However, 8-bromoguanine, lacking β-D-ribose, was found to be devoid of biological activity. Subsequent structure–activity studies revealed that substitution of the 7-nitrogen with certain aliphatic or aromatic groups enhanced immunological activity even further (Goodman and Hennen, 1986; Chen et al., 1994). The most active of the compounds tested is 7-allyl-8-oxoguanosine (7a8oGuo, loxoribine).

1.2. Overview of Cell Types Activated and Immunobiological Actions Evoked by Loxoribine and Its Analogues

Loxoribine and its analogues augment immunobiological activity of a diverse group of cell types. Perhaps the best studied of these is the B cell. The effects of loxoribine and its analogues on these cells fall into antigen-independent and antigen-dependent categories. Induction of B-cell proliferation (Goodman and Weigle, 1981, 1983d) and antigen-non-specific (polyclonal) immunoglobulin secretion (Goodman and Weigle, 1982b) fall within the former category. Also included in this group of activities is the induction of increased MHC class II molecule expression (Ahmad and Mond, 1986). These properties are best described for the earlier members of the substituted guanosine series such as 8-bromoguanosine (8BrGuo) and 8-mercaptopguanosine (8MGuo), but are most potently induced by loxoribine. Antigen-dependent effects of loxoribine and its analogues on B cells include antigen-specific enhancement of antibody responses (Goodman and Weigle, 1983b; Scheuer et al., 1985a); T-cell-like signaling to antigen-reactive B cells (Goodman and Weigle, 1983c); inhibition of tolerance induction (Scheuer et al., 1985b); and bypass of tolerant T cells late in the course of experimental tolerance (Scheuer et al., 1985b). Co-stimulus-dependent effects include the augmentation of antigen-induced proliferation of T cells (Goodman, 1991); augmentation of antigen-specific T-cell help (Goodman and Weigle, 1986); enhancement of cytolytic T-cell activity induced by poorly immunogenic stimuli (Feldbush and Ballas, 1985); inhibition of T-cell tolerance induction (Scheuer et al., 1985b); and upregulation of the secretion of certain cytokines (Goodman, 1988a; Pope et al., 1994b).

Effects on macrophages and macrophage-like cell lines have also been studied. Substituted guanine nucleosides induce these cells to secrete monokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, interferon (IFN)-α, and IL-6. Augmentation of macrophage-mediated cytotoxicity toward tumor targets was found to be only partially