CHAPTER 8

IMMUNOTHERAPEUTIC APPROACH WITH OLIGODEOXYNUCLEOTIDES CONTAINING CpG MOTIFS (CpG-ODN) IN MALIGNANT GLIOMA

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Abstract: Bacterial DNA and synthetic oligodeoxynucleotides containing CpG motifs (CpG-ODNs) are strong activators of both innate and specific immunity, driving the immune response towards the Th1 phenotype. In cancer patients, CpG-ODNs can be used to activate the innate immunity and trigger a tumor-specific immune response. Several clinical trials are on-going worldwide in various cancers. In this chapter, we will focus on the potential applications of CpG-ODNs in glioma. So far, CpG-ODN has mainly been used by intratumoral injections. Indeed, human gliomas display a locally invasive pattern of growth and rarely metastasize, making local treatment clinically relevant.

INTRODUCTION

Since the late 90s, CpG-ODNs have emerged as powerful immunostimulating agents for both innate and specific immunity. These oligodeoxynucleotides containing CpG motifs are derived from bacterial DNA and their biologic effects have been dramatically enhanced by stabilization with phosphorothioate backbones.

The immunogenic properties of CpG-ODNs have been successfully used in several experimental models of allergies, viral infections and cancers. In the last few years, CpG-ODNs have entered numerous clinical trials with vaccines against infectious diseases or for the treatment of allergies, asthma and cancer.
In cancer, CpG-ODNs have shown promising activity in multiple animal models. They can be used as a local immunostimulating agents when used alone or as an adjuvant when combined to tumor antigens, antitumor antibodies or dendritic cells. Several clinical trials are ongoing, the results of which should be available in the next few years. In this chapter, we will focus on the potential applications of CpG-ODN in glioma immunotherapy.

CpG MOTIFS

The immunogenic properties of DNA were first discovered in 1984 by a Japanese team when DNA extracts from Mycobacter tuberculosis were reported to activate natural killer (NK) cells. Subsequent works showed that the immunogenic properties were due to the presence within the bacterial DNA of CpG sequences. Interestingly, synthetic oligodeoxynucleotides containing CpG motifs display similar properties to bacterial DNA. Their biological activity is further increased if they are rendered nuclease resistant by a phosphorothioate backbone modification.

The Toll-like receptor 9 (TLR9) plays a critical role in CpG-ODN recognition. The Toll-like receptor (TLR) family is a phylogenetically conserved mediator of innate immunity that is essential for microbial recognition. In contrast to most TLRs, TLR9 has not been detected on the surface of cells and is localized in the endoplasmic reticulum prior to stimulation. No specific transporter for CpG-ODN uptake inside the cells has been identified so far. Following binding to CpG ODN, TLR9 colocalizes with CpG ODN in lysosomes.

In murine species, TLR9 is constitutively expressed in B-lymphocytes, monocytes, macrophages and all types of dendritic cells. In humans, this expression is mainly restricted to B-lymphocytes and plasmacytoid dendritic cells (DCs), although TLR9 expression has also been reported in neutrophils, monocytes, cluster differentiation (CD) 4 T cells and in some hematological malignancies.

CpG-ODNs display pleiotropic effects on the immune system reviewed by Krieg. In B cells, CpG-ODNs induce mitosis, secretion of a number of cytokines such as interleukin (IL) 6 or IL 10, prevent apoptosis triggered by several apoptotic agents and promote immunoglobulin (Ig) secretion. Plasmacytoid Dendritic Cells (pDCs) are directly activated by CpG-ODNs to express costimulatory molecules (CD40, CD80, CD86), chemokine (C-C motif) receptor (CCR) 7 and secrete a wide variety of cytokines such as tumour necrosis factor plan (TNFα), interferons (IFN), (IL)-6 or IL-12. Most interestingly, CpG-ODNs are able to “license” DCs to directly prime CD8 T cells by a (Th) cell-independent mechanism. Direct activation of NK or T cells by CpG-ODNs is unlikely. However, cytokine secretion by dendritic cells activate NK-cells and T cells, reviewed by Klinman et al. Secretion of IL12 and IFN gamma drive the T-cell differentiation towards the Th1 phenotype and can even redirect established Th2-biased to Th1 immune responses.

Several subclasses of CpG-ODNs have been described based on their in vitro activity. The “classical” B-class CpG-ODNs induce secretion of IL12, maturation of pDCs and B-cell proliferation. The biological activity of B-type CpG motifs also depends upon the 3’ and 5’ flanking bases leading to several “optimized” sequences such as 5’-GTCGTT in humans, 5’-GACGT in murine species or 5’-AAGTTT in both. The A-class is a mixed phosphodiester-phosphorothioate CpG-ODN that preferably induces IFN alpha secretion by DC and activation of NK-cells and gamma delta T cells. The C-class ODNs have immune properties intermediate between the A and B classes. So far, only the B-class has entered clinical studies.