INTRODUCTION

A great deal of progress has been made in recent decades in identifying and characterizing tumor-specific antigens that can be used as targets in immunotherapy. However, there are undoubtedly a large number of antigens that remain undiscovered. An alternative strategy to defined antigens is the use of tumor cells themselves as the source of antigen. This approach includes the broadest array of antigens but presents additional challenges that are not seen in vaccines using purified antigens such as peptides or proteins. This chapter will discuss vaccine therapy using whole tumor cells as antigen sources including not only whole cell vaccines, but also tumor cell lysate and shed antigen vaccines.

HISTORY

Efforts to develop cancer vaccines predate identification of tumor-specific antigens. One of the earliest examples is that of William Bradford Coley, a New York surgeon who noted spontaneous regression of a sarcoma after the patient developed erysipelas adjacent to the tumor. He subsequently attempted to induce such responses by injecting derivatives of bacterial cultures (“Coley’s toxins”) into the tumors of other patients [1, 2]. He did see several additional episodes of regression, but was unable to engender such responses consistently.
Early in the twentieth century, murine models of tumor vaccination were developed that utilized irradiated, whole tumor cells injected as vaccine. The mice developed protective immunity to subsequent tumor challenge. However, these studies, and others using tumor cell lysates, were performed before an understanding of histocompatibility and transplantation antigens was developed. As such a distinction between rejection of alloantigens, and tumor-specific responses could not be made.

By the middle of the century, experiments using inbred mouse strains established the immunogenicity of tumors [3]. This led to significant efforts to identify the particular tumor antigens that were recognized in these immune responses and to use these antigens in immunotherapy. The appeal of using whole tumor cells as antigen sources has remained, and several such vaccines have come into large-scale trials.

**STRATEGIES: SOURCE OF ANTIGEN**

The cellular source of vaccine antigens can be derived individually from each patient (autologous) or from pre-existing tumor cell lines (allogeneic). These tumor cells can be used whole, used after processing (e.g. by lysis) or used to produce antigens through shedding into culture supernatants. All these approaches (Figure 1) have in common a diverse array of potential epitopes for presentation to the patient’s system. Diversity may decrease the likelihood that tumors will escape immune recognition through loss of expression of vaccine epitopes. Such antigen loss has been reported with peptide-based immunotherapy [4, 5].

Vaccinated individuals also may not respond equally well to all epitopes, even when properly matched by HLA type. As an example, Reynolds et al [6] studied the spectrum of peptides to which patients vaccinated with a polyvalent, shed antigen vaccine responded. They found that, while 59% of patients responded to at least one epitope, no more than 14% of patients responded to any given specific peptide. In other words, most patients were successfully immunized, but the epitopes that the patients’ immune systems selected from the polyvalent vaccine were heterogeneous and unpredictable. This heterogeneous immune response, while probably clinically beneficial, makes monitoring of immune responses to vaccination more complex than is the case for simpler vaccine antigens.

**Live Whole Cell: Autologous**

The antigen source of a vaccine must share epitopes with those of a patient’s tumor in order to be effective. Use of the patient’s own tumor cells as the antigen source ensures optimal HLA-type matching and may maximize the number of tumor-specific antigen matches for that individual. Because of heterogeneity among metastatic lesions, it is possible that the spectrum of antigens present in the vaccine will be somewhat different from that present in the patient’s residual tumor, but, in principle this difference is least significant with autologous tumor.