1 Plasmacytomas and Hybridomas
Development and Applications

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I. Introduction

Köhler and Milstein (1975) launched a new era in immunological research by showing that somatic cell hybridization could be used to generate a continuous "hybridoma" cell line producing a monoclonal antibody. The hybridoma technology has already fulfilled one of the major goals that immunologists have been trying to achieve for years: the routine production of large amounts of homogeneous antibody against a wide variety of antigens. Each of the subsequent chapters in this monograph will illustrate the usefulness of such reagents.

Recently several investigators have shown that cell fusion can also be used to obtain cell lines that produce effector molecules of immunological interest or that respond to immunological regulation. Such hybrids may fulfill a second major goal of immunologists: to obtain homogeneous cell lines that can be used to investigate the genetic, biochemical, and molecular basis of cellular interactions in the immune response.

The development of the hybridoma technology, the approaches used to overcome technical difficulties, and the problems that still persist are reflections of the biochemistry and genetics of cell fusion and of immunoglobulin production. A brief review of some relevant experiments as well as earlier attempts to produce homogeneous antibodies provides a useful perspective. In any case, it will serve to remind us that studies with the most basic goals can lead to findings of great practical importance.
II. Experimental Uses of Plasmacytomomas

The realization that multiple myeloma is a neoplasm of antibody-producing cells and that each tumor represents the proliferation of a single clone of antibody-forming cells led to the use of paraproteins from patients to study antibody structure. The availability of an analogous tumor in mice that could be experimentally induced and passaged indefinitely provided an unlimited supply of homogeneous mouse immunoglobulins for chemical analysis (Potter, 1972). The usefulness of mouse myelomas is perhaps best appreciated by looking at the Cold Spring Harbor Symposium in 1967 on Antibodies. That volume also illustrates the enormous impact of Potter’s myeloma induction program at the NIH, and subsequently of the Salk induction program, directed by Cohn and his colleagues. Not only were the tumors themselves important, but their distribution promoted an interchange of ideas and reagents that has played a crucial role in the progress of modern immunology, culminating in the recent explosion of information on the structure of immunoglobulin genes (Seidman et al., 1978; Bernard et al., 1978; Sakano et al., 1978).

Initially the relevance of myelomas and their products to the normal immune response was questioned. This concern has been largely allayed by the finding that many myeloma proteins not only react with a variety of environmental antigens but also are serologically identical to normal antibodies generated against the same antigens (Potter, 1978). Furthermore, it has been possible to generate homogeneous antibodies against certain antigens, especially bacterial polysaccharides (Krause, 1970; Haber, 1970). The amino acid sequences of these antibodies and others have been analyzed, and the conclusions from such studies agree with studies of myeloma proteins (Cebra et al., 1974; Capra et al., 1975a,b; Haber et al., 1977). Even the synthesis and assembly of the immunoglobulin molecules in myeloma cells closely resembles these processes in normal lymphoid cells (Scharff and Laskov, 1970; Kuehl, 1977; Williamson, 1971). In fact the only reproducible difference in the metabolism of immunoglobulin in normal and malignant cells has been the kinetics of secretion, which appears to occur more rapidly and in a more ordered way in normal cells (Helmreich et al., 1961; Baumal and Scharff, 1973).

Mouse myeloma cells have been extremely useful in the study of the biochemistry of immunoglobulin production because they can be introduced into culture, cloned, and maintained as continuously growing, relatively homogeneous cultured lines (Pettengill and Sorenson, 1967; Horibata and Harris, 1970; Laskov and Scharff, 1970). These cell lines also provide an excellent somatic-cell genetic system. Variants in immunoglobulin production and structure can be obtained with relative ease (Scharff, 1974; Margulies et al., 1977), and cells producing different types of normal or variant molecules can be fused to study the interactions of genes and gene products (Margulies et al., 1977; Milstein et al., 1977). In fact the cultured myeloma cell system is unique in that the variant cells can be injected back into mice and hundreds of milligrams of the mutant gene product can be purified from the serum or the ascites of the recipient animals and sequenced (Adetugbo et al., 1977; Francus and Birshtein, 1978).