

DEVELOPMENT AND APPLICATION OF CONFORMATION-SELECTIVE INTEGRIN ANTIBODIES

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1 INTRODUCTION

1.1 Antibodies Constitute Natural Host Defense

Living organisms are continually challenged by pathogenic infections that, if allowed to persist, may result in severe disease and death. The role of the immune system is to identify, and bind to, the molecular determinants (called *epitopes*) of such pathogens, leading to their elimination from the host [1]. The challenge faced by the immune system is to identify a relatively small number of foreign substances, or antigens, against the much broader background of self and otherwise harmless or even beneficial agents (including ingested foods and pharmaceuticals). Failure to obtain sufficient discrimination between host and foreign tissue results in a wide spectrum of autoimmune pathologies, while cancer may arise, in part, due to the inability of the body to distinguish malignant from healthy cells.

The humoral adaptive immune response is mediated by soluble immunoglobulin molecules (antibodies) secreted by B cells that bind to foreign antigens and, through interactions with other components of the immune system, play a pivotal role in eliminating them from the organism [1]. The surfaces of pathogens, such as bacteria and viruses, have high molecular complexity with multiple potential (overlapping) epitopes. Each B cell secretes an antibody with a single specificity (mono-

clonal). A polyclonal response requires the participation of many B cells to provide effective coverage of the pathogen surface. The affinity of each specific antibody may differ, even against the same epitope. Through a process of clonal selection, the highest affinity antibodies are selected and become dominant in the serum.

1.2 Therapeutic Applications of Antibodies

The immune system can be modulated by the therapeutic application of antibodies with reactivity to host cell proteins. Monoclonal antibodies to human molecules can be obtained by immunization of laboratory species (such as mice) or by *in vitro* selection from synthetic libraries of antibody sequences displayed on the surfaces of microbes, such as filamentous bacteriophage [2, 3]. The origin of the antibody diversity is critical; antibodies from foreign organisms (and even purely human antibodies) can function as antigens when injected, prompting a rapid clearance and/or full immune response. Genetic engineering of the antibody sequence can be used to reduce the immunogenicity of antibodies. Native antibodies function both by blocking critical protein-protein interactions necessary for pathogen attachment and by recruiting effector cells to mediate destruction and clearance of the invading organism. Therapeutic antibodies may also be used to trigger a