Role of Monoclonal Antibodies in Neurological Disorders

Essay submitted for partial fulfillment of M.Sc. Degree in Neuropsychiatry

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LIST OF Abbreviation

AChR	:	Acetylcholine receptor
ACS	:	Acute coronary syndromes
ADCC	:	Antibody-mediated cellular cytolysis
AIS	:	Acute ischemic stroke
ANNA-1	:	Antineuronal nuclear antibody 1
APC	:	Antigen presenting cells
APCA-1	:	Anti-Purkinje cell antibody 1
ATG	:	Anti-T-lymphocyte globulin
AQP4	:	Aquaporin-4
BBB	:	Blood Brain Barier
BI	:	Barthel index
CA 19.9	:	Cancer antigens
CDC	:	Complement-dependent cytolysis
CDR	:	Complimentarily determining region
CEA	:	Carcinoembryonic antigen
CEL	:	Contrast enhanced lesion
CIDP	:	Chronic inflammatory demyelinating polyneuropathy
CIS	:	Clinically isolated syndrome
CSF	:	Cerebrospinal fluid
CVS	:	Cerebrovascular stroke
EAAT 2	:	Excitatory amino acid transporter-2
EBV	:	Epstein Barr virus
EDSS	:	Expanded disability status scale
EMG	:	Electromyography
ER	:	Endoplasmic reticulum
Fab	:	Fragment-antigen binding
Fc	:	Fragment crystalline
GPI	:	Glycoprotein IIb/IIIa inhibitors
HAT	:	Hypoxanthine-aminopterin-thymine
HGPRT	:	Hypoxanthine-guanine phosphoribosyl transferase
hIBM	:	Hereditary inclusion body myopathy
HIV	:	Human immune diffiency virus
HLA	:	Human leucocytes antigen
HTLV-1	:	Human T lymphocyte virus
IBM	:	Inclusion body myositis

ICAM	:	Intracellular adhesion molecule
Ig	:	Immunoglobulin
INCATscore	:	Inflammatory neuropathy cause and treatment score
ICH	:	Intracranial hemorrhage
IRIS	:	Immune reconstitution inflammatory syndrome
IVIg	:	Intravenous immunoglobulin
i.v.	:	Intravenously
LEMS	:	Lambert Eaton myasthenic syndrome
mAb	:	Monoclonal antibody
MAG	:	Myelin-associated glycoprotein
MBP	:	Myelin basic protein
MCA	:	Middle cerebral artery
MGT-30	:	Myasthenia gravis titin-30
MES	:	Microembolic signals
MG	:	Myasthenia gravis
MHC	:	Major histocombatibility complex
MI	:	Myocardial infarction
MIR	:	Main immunogenic region
MMN	:	Multifocal motor neuropathy
MND	:	Motor neuron disease
MOG	:	Myelin oligodendrocytes glycoprotein
mRNA	:	Messenger RNA
MRS	:	Modified rankin scale
MS	:	Multiple sclerosis
MuSK	:	Muscle-specific receptor tyrosine kinase
NIHSS	:	National institute of health stroke score
OCB	:	Oligoclonal band
JCV	:	Polyomavirus JC
PCD	:	Paraneoplastic Cerebellar Degeneration
PLEX	:	Plasma exchange
PLP	:	Protein lipid protein
PML	:	Progressive multifocal leucoencephalopathy
PNNS	:	Paraneoplastic neurological syndromes
PNS	:	Peripheral nervous system
POEMS syndrome	:	Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes

PPMS	:	Primary progressive multiple sclerosis
PRMS	:	Progressive relapsing multiple sclerosis
PTCA	:	Percutaneous transluminal coronary angioplasty
RRMS	:	Relapsing-remitting multiple sclerosis
rt-PA	:	Recombinant tissue plasminogen activator
RyR	:	Ryanodine receptor
SDS-PAGE	:	Sodium dodecyl sulfate - polyacrylamide gel electrophoresis
SPMS	:	Secondary progressive multiple sclerosis
TAP	:	Transporter associated with antigen processing
TCR	:	T-cell receptor
TIMI	:	Thrombolysis in myocardial infarction
VBA	:	Vertebra basilar artery
VCAM	:	Vascular cell adhesion molecule
VEGF	:	Vascular endothelial growth factor
VGCC	:	Voltage gated calcium channel
VLA4	:	Very-late-antigen-4

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Aim of the work:

Recent updates about role of monoclonal antibodies in pathogenesis, diagnosis and treatment of different neurological disorders for better understanding and management of these disorder.

Introduction

Antibodies are proteins produced by the B lymphocytes of the immune system in response to foreign proteins, called antigens. Antibodies function as markers, binding to the antigen so that the antigen molecules can be recognized and destroyed by phagocytes. The part of the antigen that the antibody binds to is called the epitope. The epitope is thus a short amino acid sequence that the antibody is able to recognize ***(Campbell, 1996).***

Each B cell in an organism synthesizes only one kind of antibody. There is an entire population of different types of B cells and their respective antibodies that were produced in response to the various antigens that the organism had been exposed to. However to be useful as a tool, molecular biologists need substantial amounts of a single antibody. Therefore we need a method to culture a population of B cells derived from a single ancestral B cell, so that this population of B cells would allow us to harvest a single kind of antibody. This population of cells would be correctly described as monoclonal, and the antibodies produced by this population of B cells are called monoclonal antibodies (mAb) ***(Fratella et al, 1998).***

There is evidence that B cells are involved in the pathophysiology of many neurological diseases, either in a causative or contributory role, via production of autoantibodies, cytokine secretion, or by acting as antigen-presenting cells leading to T cell activation. Also it has diagnostic role as once monoclonal antibodies for a given substance have been produced, they can be used to detect the presence of this substance ***(Schmitz et al, 2000).***

Moreover, the role of mAb therapies in treating medical conditions has expanded tremendously since its inception in the 1970s, and their use in neurologic conditions has increased in just the past few years, multiple sclerosis, neuromyelitis optica, myasthenia gravis, inclusion-body myositis, cerebrovascular stroke, peripheral neuropathy, Paraneoplastic syndromes and central nervous system lymphoma ***(Novak et al, 2008).***

Definition of Monoclonal antibody:

It is an antibody produced by a single clone of cells (specifically, a single clone of hybridoma cells) and therefore a single pure homogeneous type of antibody. Monoclonal antibodies can be made in large amounts in the laboratory and are a cornerstone of immunology ***(Eleonora et al, 2003).***

History:

In 1975 Cesar Milstein and Georges Kohler, working at the University of Cambridge, devised a laboratory technique for making monoclonal antibodies **(mAb)**. They wanted to have long-lived cell lines that would make antibodies of a single kind. Antibody producing cells could be harvested from the spleen of mice that had been exposed to a known antigenic protein but these cells only grew transiently in the laboratory. They also had mouse myeloma cells, tumor cells that would grow indefinitely in the laboratory and produce immunoglobulin, the substance of antibody, but not make a pure antibody. They fused the mouse spleen cells with the mouse myeloma cells in the hope that one would bring to the union the antibody specificity they needed ***(Kohler et al, 1975).***

A process of producing **(mAb)** involving human-mouse hybrid cells was described by Jerrold Schwaber in 1973 ***(Schwaber et al, 1973).*** The invention is generally accredited to Georges Kohler and his college in 1975***;*** who shared the Nobel Prize in Physiology of Medicine in 1984 for this discovery. The key idea was to use a line of myeloma cells that had lost their ability to secrete antibodies, come up with a technique to fuse these cells with healthy antibody-producing B-cells, and be able to select for the successfully fused cells ***(Kohler et al, 1975).***

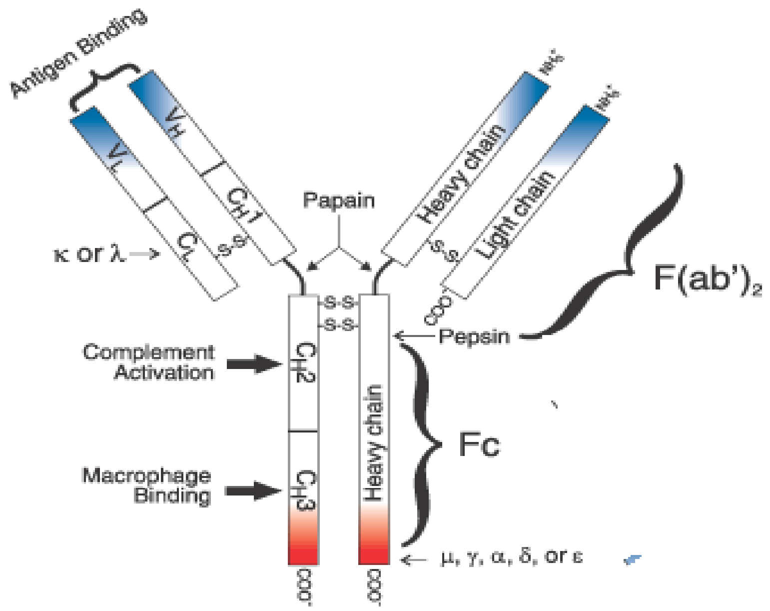
Discovery:

The idea of a "magic bullet" was first proposed by Paul Ehrlich who at the beginning of the 20th century postulated that if a compound could be made that selectively targeted a disease-causing organism, and then a toxin for that organism could be delivered along with the agent of selectivity ***(Robert et al, 2004).***

In the 1970s the B-cell cancer multiple myeloma was known, and it was understood that these cancerous B-cells all produce a single type of antibody. This was used to study the structure of antibodies, but it was not yet possible to produce identical antibodies specific to a given antigen ***(Schmitz et al, 2000)***.

Structure and function of human and therapeutic antibodies:

Immunoglobulin G (IgG) antibodies are large heterodimeric molecules, approximately 150 kDa and are composed of two different kinds of polypeptide chain, called the heavy chain (~50kDa) and the light chain (~25kDa). There are two types of light chains, kappa (κ) and lambda (λ). By cleavage with the enzyme papain, the Fab (*fragment-antigen binding*) part can be separated from the Fc (*fragment crystalline*) part of the molecule (Figure 1). The Fab fragments contain the variable domains, which consist of three hyper variable amino acid domains responsible for the antibody specificity embedded into constant regions. There are four known IgG subclasses, all of which are involved in antibody dependent cellular cytotoxicity ***(Janeway et al, 2001).***



(Figure 1) structure of antibody ***(Mark Shlomchik, 2001).***

Antibodies are a key component of the adaptive immune response, playing a central role in both the recognition of foreign antigens and the stimulation of an immune response to them. The advent of mAb antibody technology has made it possible to raise antibodies against specific antigens presented on the surfaces of tumors ***(Janeway et al, 2005).***