CHAPTER 1

INTRODUCTION

1.1 Background

The Epstein-Barr virus (EBV) is one of the most common viruses in humans. Infection Epstein-Barr virus continues a lifetime after primary contact and the virus is spread throughout the world in about 90% of all humans. Usually EBV infection is not causing any health problems but in certain individuals EBV can cause various diseases from acute inflammatory illness such as chronic EBV infection, infectious mononucleosis or to lymphoid and epithelial cancers and diverse autoimmune diseases. A strong immune response is able to control EBV activity starting from the first contact. The action of NK cells, T cells and antibody response of IgM, IgG and IgA address different viral antigens. Abnormal viral activity is reflected in aberrant immune responses, which can be measured in vitro by using a patient sample (blood or serum / plasma).

EBV is causally associated with nasopharyngeal carcinoma (NPC) and aberrant IgG and IgA antibody responses can be detected at early stages of disease development and have diagnostic importance (Fachiroh et al., 2004). These antibodies recognize a range of viral antigens, exceeding the "normal" range of reactivity (diversity). Whereas IgG responses are considered to reflect systemic immune control, IgA antibodies reflect mucosal immune responses at body surfaces produced by specialized (Nasal/Gut/Bronchus) mucosa-associated lymphoid tissue (MALT or NALT/GALT/BALT).

In routine diagnostic settings no clear functional aspect is considered for IgG and IgA responses, but it is clear that multiple EBV antigens (proteins and epitopes) are involved in such responses, being either the VCA, EAd or EBNA complex. Previous research has found that Zebra and viral membrane antigens can also be used as marker to detect EBV (Middeldorp, 2015).

However, analysis of the relation between antigen specificity of IgG and IgA responses has not received much detailed attention. IgG and IgA antibodies may recognize different viral protein antigens, reflecting different antigen-activity and immune triggering events during persistence or disease development, or may differ in epitope recognition, reflecting independent antigen-processing and presentation for IgG versus IgA B-cell responses. This analysis may reveal aberrant virus activity (systemic versus mucosal) at early NPC stages triggering such responses and underlying the pathogenesis of the NPC disease.

IgG and IgA were used in this study because IgG is the main immunoglobulin that circulates both in intravascular and extravascular spaces such as blood, lymph fluid, cerebrospinal fluid, and peritoneal fluid. IgG in adult human serum is about 15% of total serum proteins (other proteins including albumin, globulin, and enzymes) and as a versatile antibody competently performing various functions from neutralizing toxins and viruses to complement and opsonization activation. IgG antibodies are efficient antibodies to the virus. One of the neutralization mechanisms is that antibodies bind to the antigenic determinants present in the virus layer, between those areas used by the virus to

stick to the target cells. Versatility in the functioning of IgG molecules makes it a very important molecule in the immune response (Male et al., 2013).

While IgA is found in serum as a monomeric molecule. The dimeric IgA found in secretions is known as secretory IgA. Secretory IgA in saliva and intestinal fluids is an important antiviral immunoglobulin. Most IgA dimers are not found in serum, but in secretions such as tears, saliva, sweat, and mucus, where it has an important biological role as part of the mucosal-linked lymphoid tissue (MALT). Because of its presence in secretions, such as saliva, urine, and gastric juices, secretory IgA is important in primary immunological defense against respiratory or local gastrointestinal infections. IgA antibodies, induced by vaccination can prevent attachment and penetration of the epithelial surface of the organism. IgA secretory is an efficient antiviral antibody, preventing the virus from entering host cells (Male et al., 2013).

1.2 Problem Formulation

Based on the background that has been described above, the problem formulation in this study is to analyze the antigen-recognition specificity of IgG and IgA responses in patients with the NPC disease.

1.3 Research Purposes

1.3.1 General Purpose

It is the aim of this study to further characterize the antigen and epitope diversity of human anti-EBV IgG and IgA responses, especially in NPC patients from Indonesia and the Netherlands versus healthy controls.

1.3.2 Specific Purpose

The specific aims of this research are:

1) Defining correlation between IgG and IgA against VCA P18 and EBNA1 immunodominant multi-epitope peptide antigens
2) Comparing IgG and IgA epitope reactivities within the Zebra protein (peptides vs. recombinant).

1.4 Benefits

1.4.1 Theoretical Benefits

The result of this study may be scientific informative about the diversity of antigen and epitope recognition of human anti-EBV IgG and IgA responses, comparing NPC patients from Indonesia and the Netherlands.

1.4.2 Practical Benefits

Knowledge on various proteins or epitope triggering human anti-EBV IgG and IgA is expected to be utilized in the development of diagnostic tests to improve detection of NPC at early stages of the disease.