Polymorphisms of the drug-metabolizing enzyme *CYP1A1* and susceptibility to B-cell Non-Hodgkin lymphoma

Thesis

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ABSRACT

BACKGROUND: The incidence of NHL has been steadily rising as a possible result of environmental carcinogens exposure. OBJECTIVE: We aimed at determining whether polymorphisms of drug-metabolizing enzyme CYP1A1 increase susceptibility to B-cell NHL. METHODS: Two CYP1A1 gene polymorphisms (3801 [T>C] and 4889 [A>G]) were analyzed in 50 DLBCL patients and 25 controls using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). RESULTS: CYP1A1*2C allele ($p<0.001$, OR: 6.1, 95% CI: 2.5-14.95) demonstrated highly significant association with DLBCL compared to controls. CONCLUSION: CYP1A1*2C is a risk factor for DLBCL.

KEYWORDS: drug-metabolizing enzyme, CYP1A1, polymorphism, DLBCL.

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LIST OF ABBRIVIATION

AHH: Aryl hydrocarbon hydroxylase.
ARNT: Ah receptor nuclear translocator.
ASO: Allele Specific Oligonucleotide.
bp: Base paire.
CBC: Complete blood count.
CLL: Chronic Lymphocytic Leukemia.
CO: Carbon monoxide.
CR : complete remission**.**
Cth : chemotherapy.
CYP450: Cytochrome P450.
dATP: Deoxy adenine triphosphate.
dCTP: Deoxy cytosine triphosphate.
ddNTP : Dideoxynucleotides triphosphate.
DHEAS: Dehydro-epiandrosterone sulfate.
DLBCL: Diffuse Large B-cell Lymphoma.
DNA: Deoxyribonucleic acid.
dNTP : Deoxy nucleoside triphosphate.
dTTP : Deoxy thiamine triphosphate.
EDTA: Ethylenediaminetetraacetic acid.
EGF: Epidermal growth factor.
ER: Endoplasmic reticulum.
FAD: Flavin adenine dinucleotide.
FMN: Flavin mononucleotide.
FMO: Flavin mono-oxygenase.
GSTs: Glutathione S-transferases.
KDa: Kilo Dalton.
m RNA : Messenger ribonucleic acid
Msp I: Moraxella species.
NADPH: Reduced Nicotinamide adenine dinucleotide phosphate.
NAT: N-acetyltransferases.
NF: Nuclear factor.
NHL: Non Hodgkin Lymphoma.

PAPs: 3- phosphadenosine 5´-phosphosulfate.
PAHs: Polycyclic aromatic hydrocarbon.
PCR: Polymerase chain reaction.
PON1: Paraoxonase.
PR: Partial response**.**
RFLP: Restriction Fragment length polymorphism.
Rth : radiotherapy
SULTs: Sulfotransferases.
SLL: Small-cell Lymphocytic leukemia.
Taq: Thermus aquaticus.
UADT: Upper Aerodigestive Tract.
UGTs: UDP glycosyltransferases.
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Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous malignancy of B- and T-cells that involves their uncontrolled clonal expansion in the periphery. B-cell lymphomas make up the majority of cases and, of these, diffuse large B-cell lymphoma (DLCL) and follicular lymphoma (FL) are the two major subtypes ***(Skibola et al., 2007)***.

The incidence of non-Hodgkin's lymphoma (NHL) overall has been steadily rising since the 1950s ***(Alexander et al., 2007)***. Several environmental and occupational exposures have been suspected as risk factors for NHL. Increased incidence has been consistently observed among farmers ***(De Roos et al., 2006).*** Associations with exposure to herbicides and pesticides, benzene and other solvents, dioxins and other potentially DNA-damaging agents have been reported, although the findings have been inconsistent ***(Shen et al., 2007)***.

DNA damage in the hematopoietic precursor cell is the essential prerequisite for the development of leukemia and the body has developed a series of mechanism aimed at preventing such damage. It has been suggested that individuals possessing a

modified enzyme ability to metabolize carcinogens are at increased risk of cancer. In other words gene polymorphisms of these enzymes may lead to a more active enzyme form resulting in carcinogen activation or alleles with less efficient detoxification and thus greater susceptibility to cancer ***(Aydin-Sayitoglu et al., 2006).*** Humans vary in their ability to detoxify intermediates, which in theory may explain differences in leukemia risk as a result of exogenous exposure ***(Bajpai et al., 2007)***.

The cytochrome P 450 (CYP) superfamily is one of two major phases catalyzing oxidative metabolism. Numerous genetic polymorphisms have been reported for **CYP** indicating a lack of functional protein or causing either increased or reduced metabolic activity ***(Dufour et al., 2005)***. **CYP1A1** catalyzes the oxidation of polycyclin aromatic hydrocarbons [PAH] to epoxides. **CYP1A1** polymorphism has been studied in relation to cancer susceptibility including hematological malignancies like acute leukemias and chronic myeloid leukemia ***(Bajpai et al., 2007)*** and may mediate the risk of non-Hodgkin's lymphoma ***(De Roos et al., 2006)***.

Aim of the work

The aim of this work is to investigate the effect of inherited genetic polymorphisms of the drug-metabolizing enzyme CYP1A1 (3801 [T→ C] and 4889 [A→G]) on a predisposition to B-cell Non- Hodgkin's Lymphoma.

CHAPTER 1

Xenobiotics

Xenobiotics are chemical compounds synthesized by man which are not naturally found in living organism and can not normally be metabolized by them.

The xenobiotics have molecular structure and chemical bond sequence not recognized by existing degenerative enzymes.

All organisms are exposed constantly and unavoidably to foreign chemicals, or xenobiotics, which include both man-made and natural chemicals such as drugs, industrial chemicals, pesticides, pollutants, pyrolysis products in cooked food, alkaloids, secondary plant metabolites, and toxins produced by molds, plants and animals. The physical property that enables many xenobiotics to be absorbed through the skin, lungs, or gastrointestinal tract, namely their lipophilicity, is an obstacle to their elimination because lipophilic compounds can be readily reabsorbed. Consequently, the elimination of xenobiotics often depends on their conversion to water-soluble compounds by a process known as biotransformation, which is catalyzed by enzymes in the liver and other tissues.

The activity of these enzymes varies broadly between individuals from absence to high activity and this variance can be responsible for adverse or toxic effects of drugs and xenobiotics or plays a key role in the etiopathology of several malignancies. Their enzymatic activities depend on hereditary