UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL SCHOOL

DOCTORAL THESIS
SUMMARY

PROMOTER:
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Craiova

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UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
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AUTOPHAGY INVOLVMENT IN TUBERCULOSIS

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Introduction:

Tuberculosis is one of the oldest diseases that has affected humanity and has been discovered since antiquity [1]. The identified skeleton fragments suggest that tuberculosis was present in prehistoric people (4,000 BC) [1].

Francis Sylvius de la Böe (1614-1672) was the first to make the anatomo-pathological description and claimed that pulmonary tuberculosis evolves in three stages:

- inflammation (tuber formation),
- ulceration and
- ftizis, the latter, which was also confirmed by Richard Morton who described a relationship between glands, tubers, and lung consumption. The two state that the disease is hereditary.

The first to visualize Mycobacterium was Gerhard Hansen (1873), Mycobacterium leprae, but could not prove the cause.

The infectious etiology of tuberculosis was controversial until 1882 when Robert Koch discovered the tuberculosis bacillus, which also bears his name and implemented new techniques for obtaining pure mycobacterial cultures.

Pulmonary tuberculosis is transmitted by air, from an ill person to a healthy person, via droplet drops [2].

Persons who have prolonged, frequent, or close contact with people with tuberculosis are at high risk of infection, with an estimated infection rate of 22% [3].

Tuberculosis, declared by the World Health Organization at the beginning of the 21st century as a global emergency, still constitutes, despite progress in diagnosis, treatment and follow-up of the disease, a major challenge for health services around the world [4-6].

Moreover, TB is still in the group of the top ten deaths worldwide, estimated that around 1.5 million people die annually because of this disease [7.8].

On the other hand, autophagy is considered as a response to extra- or intracellular stress and to signals such as hunger, lack of growth factor, endoplasmic reticulum stress and pathogenic infection [9].

Incorrect autophagy plays a significant role in human pathologies, including cancer, neurodegeneration and infectious diseases.

In this context, our study aims to evaluate the association of polymorphisms identified in genes involved in the autophagy process, such as ATG5 and NOD2, and susceptibility to pulmonary tuberculosis in Eastern Europe (Romania), a region where these genetic variants Have been investigated so far.

Key words: pulmonary tuberculosis, single nucleotide polymorphisms, genotype, susceptibility

I THE STAGE OF KNOWLEDGE

Chapter 1. **HISTORY OF TUBERCULOSIS** presents concrete information about what is pulmonary tuberculosis when the first signs of this disease were discovered and its anatapathological description was made. Further in this chapter is presented the evolution of treatment and preventive BCG vaccination measures.

In Chapter 2, Epidemiology, there is recent data on incidence and mortality rates for pulmonary tuberculosis. This chapter highlights the differences between different regions of the globe and then at the level of the European continent.

Chapter 3. Autophagia refers to the fact that autophagy is a process of self-degradation of cellular components in which double membrane autophagosomes secrete organisms or portions of cytosol and fuse with lysosomes for degradation using hydrolases being considered as a response to extra - or intracellular signals and signals such as hunger, lack of growth factor, endoplasmic reticulum stress, and pathogenic infection.

II. PERSONAL CONTRIBUTIONS

Chapter 4. PURPOSE AND OBJECTIVES

Our study started from the analysis of the frequency of the main polymorphisms in the genes involved in the mechanism of action of the autophagy process, as well as modulating genes of this mechanism on two groups of subjects. A group of subjects with active or past pulmonary tuberculosis and a second control batch. The purpose of the study was to correlate the allelic variants for the polymorphisms studied in the two groups with the decrease or, on the contrary, the increase in susceptibility to pulmonary tuberculosis in an Eastern European population, respectively from Romania.

Objectives of the study:

1. Determination of the frequency of allelic variants for polymorphism of studied ATG5 gene,

2. Determination of the frequency of allelic variants for polymorphism of studied NOD2 gene,

3. Correlation of results and determination of association of allelic variants studied with change in susceptibility to pulmonary tuberculosis.

All the objectives of this study have been successfully completed.

Chapter 5. MATERIAL AND METHOD

For this study, a total of 586 subjects were enrolled in two study groups, namely the TB group and the Control group. For the TB group, 256 uninvolved subjects were enrolled, diagnosed with active pulmonary tuberculosis or with a history of pulmonary tuberculosis. In the Control group, 330 subjects were enrolled without active or antecedent pulmonary tuberculosis. Determination of allelic variants was done by Real-Time PCR using two systems, namely ViiA7 (Life Technologies, Carlsbad, USA) and RotorGene 6000 HRM-Corbett respectively, using the TaqMan-specific probes for the two desired polymorphisms, namely ATG5 rs2245214 .574-12777G> C) and NOD2 rs2066844 (c2104C> T).

Chapter 6. RESULTS

For the TB group, 256 uninvolved subjects were enrolled, diagnosed with active pulmonary tuberculosis or with a history of pulmonary tuberculosis. Subjects were diagnosed according to national standards recommended by the National Tuberculosis Control Program.

In the Control group, 330 subjects were enrolled without active or previous pulmonary tuberculosis compared to age group TB.

The results were interpreted based on the amplification curve generated by the increase in the chemiluminescent signal from the dyes used but also by comparing the absolute values of the signal of the two dyes read by the two Real Time PCR systems used (ViiA7 - Life Technologies, Carlsbad, USA; Respectively RotorGene 6000 HRM-Corbett). Thus, using the TaqMan probe, the allelic variants were identified: C using the VIC and G dye using the FAM dye and the genotypes that form CC, CG and GG for the ATG5 polymorphism rs2245214 (c.574-12777G> C) , Respectively C using the VIC and T dye using the FAM dye and the genotypes that CC, CT and TT form for the NOD2 polymorphism rs2066844 (c2104C> T). The results obtained by studying the two lots, TB and Control, are summarized in the tables below.

ATG5 rs2245214	Genotype	TB	Control	CHI2, df	p
	CC	121	151		
	CG	101	131		
	GG	34	43		
G vs. C				0.04624, 2	0.9771

Frequency of ATG5 rs2245214 (c.574-12777G>C) polimorphism

NOD2 rs2066844	Genotype	TB	Control	CHI2, df	p
	CC	240	307		
	CT	16	22		
	TT	0	1		
T vs. C				0.8224, 2	0.6629

Frequency of NOD2 rs2066844 (c.2104C>T) polymorphism

To have a better overall picture, we continued the dominant and recessive pattern analysis between genotype and phenotype, the results being presented in the tables below. Thus, the minor G allele of the ATG5 interstitial polymorphism rs2245214 (c.574-12777G> C) recorded comparable frequencies between the two batches analyzed, namely 33.01% in the TB group and 33.38% in the control group, also the minor T allele of the polymorphism " Missense "NOD2 rs2066844 (c.2104C>

T) recorded comparable frequencies between the two groups analyzed, namely 3.13% in the TB group and 3.64% in the control group. These frequencies are similar to those present in the European population, as shown by the study of the "1000 genomes" study.

ATG5 rs2245214 (c.574-12777G>C)

Genotype	TB (%, n)	Control (%, n)
CC	20.83%, 121	25.99%, 151
CG	17.83%, 101	22.55%, 131
GG	5.85%, 34	7.4%, 43
Dominant model OR 0.9956, p = 0.9858		
Recessive model OR 1.0328, p = 0.8471		

Analysis of dominant and recessive model for ATG5 rs2245214 (c.574-12777G>C)

NOD2 rs2066844 (c.2104C>T)

Genotype	TB (%, n)	Control (%, n)
CC	40.96%, 240	52.39%, 307
CT	2.73%, 16	3.75%, 22
TT	0	0.17%, 1
Dominant model OR 2.3354, p = 0.6040		
Recessive model OR 1.1238, p = 0.7289		

Analysis of dominant and recessive model for NOD2 rs2066844 (c.2104C>T)

Chapter 7. DISCUSSIONS

Pulmonary tuberculosis, caused by infection with Mycobacterium tuberculosis bacillus, is the leading cause of infectious death in the world.

The World Health Organization [7] reported more than 9.6 million new cases of tuberculosis in 2014. In the same year, 1.5 million patients died of this severe infection.

Mycobacterium tuberculosis is transmitted between humans, mainly by the droplets from aerosols generated by patients with active pulmonary disease. It can invade, persist and replicate inside the macrophages by stopping the phagosome maturation and inhibiting lysozyme - phagosome fusion [10].

Macrophages can control this evasion by inducing autophagy, an elaborate cellular process in which cytoplasmic content, including bacilli, is directed to lysosomal degradation, thereby reducing bacterial load in infected cells [10, 11].

Autophagia, a process preserved during evolution, mediates the degradation of deficient organisms or proteins under stress or lack of energy of the eukaryotic cell in order to generate the necessary nutrients [12, 13].

Autophagy has been shown to also modulate inflammation in the innate immune system as well as acquired immune response [14].

Autophagy works by forming a double membrane structure called autofagosome that sequesters the cytosolic material and subsequently merges with the lysosome to degrade and then release the resulting products into the cytosol [12].

This process is regulated by a specific set of the genes related to autophagy (ATG) family [103]. Once the autophagy process is induced, different components of the autophagy pathway, such as ATG5, ATG12, ATG16 and LC3, cooperate to form autophagosomes and deliver sequestered material to lysozom [15].

ATG5 is a central regulatory gene in the autophagous process, being involved in the elongation of the autophagosomal membrane [9, 16].

In addition, NOD2 (CARD15 or NLRC2) is an important member of the NLR gene family expressed in macrophages, granulocytes and monocytes [17], which recognizes both gram-positive and gram negative bacteria [18, 19]and have an important role in controlling the process of autophagy [20].

A clear involvement of NOD2 in the recognition of Mycobacterium tuberculosis has been demonstrated in NOD2 - / - [21] mice strains.

On the other hand, the role of autophagy for the host's anti-mycobacterial defense was triggered by a recent study. It confirmed that ATG5 plays an important role in the host response to mycobacterial infection by restricting Mycobacterium tuberculosis growth, which has raised the role of autophagy in this process [10].

To investigate the role of autophagy in host defense against tuberculosis in humans, we assumed that genetic variants, such as the mononucleotide polymorphisms of the ATG5 - rs2245214 (c.574-12777G> C) genes and NOD2 - rs2066844 (c.2104C> T), are associated with susceptibility to active pulmonary tuberculosis.

Autophagy was considered a new and promising pathway, a target for the development of better vaccines and new drugs designed to eliminate Mycobacterium tuberculosis [22-25]. Recent studies have raised this hypothesis [10].

An important approach in assessing the role of certain processes for host defense against tuberculosis in humans is to investigate whether the genetic profile influences susceptibility to infection.

Of the ATG gene family, ATG5 is an important modulator of the autophagy process, tasked with expanding and closing the double membrane structure called autofagosome [26].

There are both in-vivo and in-vitro studies, focused on autophagy and, more specifically, on the ATG5 gene and its implication in tuberculosis. Studies provide different outcomes for in-vivo approach. Thus, there is either a modest deficiency in control of the macrophage after infection in strains of mice that do not have ATG5 in myeloid cells [27] or a severe one leading to a higher level of bacteria and faster death [10, 28].

These findings indicate that autophagy and the ATG5 gene are essential for the in vivo control of Mycobacterium tuberculosis. However, no clear conclusions could be drawn regarding the role of genetic polymorphisms in the ATG5 gene. Some

studies suggest an impact on susceptibility to pulmonary tuberculosis [10], although they have failed to reproduce this [29]. In this study, we tried to investigate this hypothesis in a Romanian tuberculosis cohort, but the influence on susceptibility to infection could not be noticed.

In addition, little is known about the susceptibility to tuberculosis of persons carrying allelic variants in the NOD2 gene. The potential role played by the NOD2 gene in TB infection has been suggested by two studies that highlighted the involvement of this gene in the recognition of Mycobacterium tuberculosis by signaling the production of proinflammatory cytokines [18, 21].

Recent studies have shown that NOD2 modulated signaling may initiate the autophagy response [30], which seals intracellular bacteria in autophagosome [20] and limits infection [31]. NOD2 rs2066844 has been associated in several studies with susceptibility to other chronic pathological conditions such as Crohn's disease [32-35], schizophrenia [36] and asthma [37].

However, we could not identify an association between the NOD2 rs2066844 polymorphism (c.2104C> T) and the increased risk of developing active pulmonary tuberculosis. This observation, coupled with the absence of association of genetic variants of ATG5 polymorphism rs2245214 (c.574-12777G> C), suggests that autophagy and Mycobacterium tuberculosis have a complex interaction [29] and that the autophagy process can be redundant for host defense against tuberculosis, as has been suggested recently [10].

A limitation of the present study is represented by the size of the cohorts, which were not sufficient to exclude the role of the genetic variants of the ATG5 and NOD2 genes in pulmonary tuberculosis. In addition, since this study included both subjects with recently diagnosed active pulmonary tuberculosis and those with a history of TB, this did not allow the evaluation of the influence of ATG5 and NOD2 genotypes on the severity of the disease.

Chapter 8. CONCLUSIONS

This is the first study to evaluate the role of polymorphisms of genes involved in autophagy in an East European population with many cases of pulmonary tuberculosis.

The results obtained in this study suggest that ATG5 and NOD2 genotypes are not associated with the risk of developing active pulmonary tuberculosis.

Also, no evidence of an interaction between the genotypic variants of ATG5 rs2245214 and NOD2 rs2066844 was found.

The lack of association between the polymorphisms studied and the susceptibility to pulmonary tuberculosis found in this study does not rule out the possibility that other mononucleotide polymorphisms from the two genes (or other genes involved in autophagy) contribute to the risk of developing active pulmonary tuberculosis.

The limitations of the study are related to:

- the size of cohorts, which were not sufficient to exclude the role of genetic variants of ATG5 and NOD2 genes in pulmonary tuberculosis.
- The fact that this study included both subjects with recently diagnosed active pulmonary tuberculosis and those with a history of TB did not allow the evaluation of the influence of ATG5 and NOD2 genotypes on the severity of the disease.

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