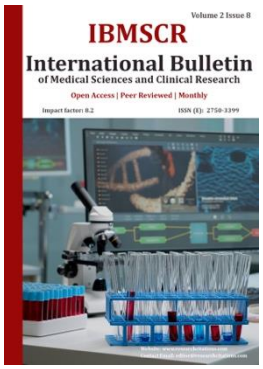

ANATOMICAL STRUCTURE OF THE LIVER

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Abstract. He proportion of elderly people in the world population is constantly increasing. With age, the risk of numerous chronic diseases and their complications also rises. Research on the subject of cellular senescence date back to the middle of the last century, and today we know that senescent cells have different morphology, metabolism, phenotypes and many other characteristics. Their main feature is the development of senescence-associated secretory phenotype (SASP), whose pro-inflammatory components affect tissues and organs, and increases the possibility of age-related diseases. The liver is the main metabolic organ of our body, and the results of previous research indicate that its regenerative capacity is greater and that it ages more slowly compared to other organs. With age, liver cells change under the influence of various stressors and the risk of developing chronic liver diseases such as non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH) and hepatocellular carcinoma (HCC) increases. It has been proven that these diseases progress faster in the elderly population and in some cases lead to end-stage liver disease that requires transplantation. The treatment of elderly people with chronic liver diseases is a challenge and requires an individual approach as well as new research that will reveal other safe and effective therapeutic modalities.

Key words: cell, senescence, SASP, DDR, inflammaging, liver, elderly

Introduction. According to the results of recent research, the world population is getting older. The incidence of many diseases increases with age, and the basis of some of them may be changes which are associated with aging [1,2]. That is why we call them age-related diseases. This is one of the reasons why the number of investigations of cellular senescence is rising**.**

The first studies of cellular senescence date back to the middle of the last century [3,4]. Cellular senescence is a permanent cell cycle arrest that reduces the proliferative and regenerative capacity of cells [5]. It can be caused by various factors such as telomere dysfunction, deoxyribonucleic acid (DNA) damage, oxidative stress, oncogenic activity, etc. [5]. The most common cause of the induction of senescence is the activation of a DNA-damage response [6]. The metabolism of senescent cells is distinct from non-senescent cells and they are metabolically active regardless of the cell cycle arrest [7]. These phenotypically altered cells secrete various molecules, primarily cytokines, chemokines and proteases which make the senescence-associated secretory phenotype (SASP). SASP has numerous roles in the human body and its components affect surrounding cells paracrine [8]. These molecules have been detected in numerous studies, mostly in vitro, and can serve as markers of senescence [3]. The determination of these markers can help in the recognition of senescent cells, as well as in a potential therapeutic approach to age-related diseases [1,9]. Considering that in these conditions the production of pro-inflammatory cytokines is increased, the term

"inflammaging" was introduced into the literature [1,8]. The consequences of cell aging are present in all tissues and organs and progress at different speeds depending on the type of tissue or organ, gender and the effects of endogenous and exogenous factors. The liver is a metabolic and endocrine active organ that is often called "the laboratory of the organism" and the first research on the topic of its aging dates back to the end of the last century [10]. It has been proven that the incidence of liver diseases, as well as mortality from these diseases, increases with age [11]. Age is often an independent factor of poor outcomes in liver diseases [12]. In this connection, the pathophysiology of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), viral hepatitis and hepatocellular carcinoma (HCC) in elderly patients was examined [12,13,14]. Based on the results of these studies, it was concluded that due to proven differences between younger and older people with these diseases, the treatment of patients must be approached individually.

In the 1960s, Hayflick and Moorhead were the first to describe the concept of cellular senescence by observing human diploid fibroblasts [3,4]. Considering the importance of such discovery, researchers from different fields of natural sciences tried to investigate this phenomenon in more detail. It has been shown that cellular senescence is related to diseases that accompany aging, so new achievements in this area could enable the prevention of these diseases, better survival and longer life expectancy of the people [3]. Cellular senescence corresponds to an irreversible stable cell cycle arrest that limits cell proliferation and promotes chronic inflammation [4]. Still, it is not known if the cellular senescence can, potentially, be reversible, but if confirmed, this would be of great importance especially in oncology as senescent cells appear to be particularly important for relapse of malignancies. As a response to various forms of chemotherapy, cells enter senescence. However, it has been shown that tumor cells are able to avoid that fate by different mechanisms. In this way, they manage to enter a specific state of rest and to live longer despite the use of chemotherapeutic agents, which increases the possibility of recurrence of the malignant disease [15,16]. An example from clinical practice is the ability of some breast cancer cells to avoid the effect of an adequate concentration of doxorubicin, as well as the ability of some lung cancer cells to bypass the entry into senescence caused by the administration of camptothecin [17,18]. Studies have shown that the cell's ability for this process depends on the expression of the cyclin-dependent kinase [15]. On the other hand, Zampetidis et al. are of the opinion that the possibility of avoiding entry into senescence is a consequence of genome instability [19]. Senescence represents the cell's response to numerous stressors [20]. The causes for the initiation of cellular senescence, i.e., the stressors that induce its onset, are different, but the most commonly discussed are the effects of DNA damage, oxidative stress, oncogenic activity and chemotherapeutic toxicity [20]. In this process, cells undergo epigenetic, transcriptional, metabolic and morphological changes [8]. As long as cell damage by these factors does not cause permanent cell cycle arrest, the cell is not considered senescent [3]. Induction of cellular senescence is unidirectional and irreversible, which means that once it starts, there is no return to the initial state, and there is no way for the cell to return to any of the stages that precede the entry into senescence [3]. During this process, there is a decrease in the proliferative capacity of cells, a decrease in the number of cells and the accumulation of cellular debris, which promotes tissue damage and reduces the possibility of tissue regeneration [1,8]. It is important to understand that senescence is not a single program, such as, for example, the apoptotic program, but includes a variety of effector mechanisms [21].

These mechanisms are also found in other cellular processes, so they are not specific to cellular senescence. For example, there is the concept of reproductive senescence, oncogene-induced senescence, etc. [22]. Although senescence is most often associated with a negative aspect, as it is related to age-related diseases, it also has a significant irreplaceable non-pathological role in, for example, the process of embryogenesis [8,23,24]. The largest number of tests on the topic of cellular senescence were performed in vitro [3]. It has been shown that senescent cells have several common features: prolonged cell cycle, increased cell soma size, metabolic changes, telomere shortening and intracellular damage [3,7,25]. Gorgoulis et al. defined that the hallmarks of senescence phenotype are cell cycle withdrawal, macromolecular damage, secretory phenotype and dysregulated metabolism [26]. A prolonged cell cycle delays the entry of the cell into the phase of division thereby reducing its reproductive capacity [3,7,26]. Tests performed on human diploid fibroblasts prove this. A decrease in cell proliferative power is accompanied by an increase in size gradually during the aging process [27,28]. In addition, in order for the cell cycle to proceed smoothly, it is necessary that many metabolic pathways function in an efficient manner [4]. In cells that are in the process of senescence, significant changes occur in the metabolic pathways of almost all macromolecules [4,20]. Some of the most significant changes are an increase in the level of glycolysis, a decrease in the capacity for oxidative phosphorylation and a decrease in the level of nicotinamide adenine dinucleotide (NAD), intracellularly [29,30,31]. These changes also affect the clonal ability of the cells and their importance can be understood through the study results. In vivo research on a murine lymphoma model in which cellular senescence was initiated by chemotherapy proved that tumor regression occurs by blocking glycolysis [32]. Another study showed that the supplementation of cells with NAD precursors increases reproductive lifespan and replicative capacity [33,34]. In addition to the above, it is important to mention that senescent cells are characterized by progressive telomere shortening [6,35,36]. They represent complexes of nucleoproteins which are protecting the ends of chromosomes from the action of enzymes [37]. They are built from special tandem repeats (5′-TTAGGG-3′) and are associated with multiprotein complexes called shelterin [37]. The role of shelterin is to protect the ends of chromosomes from damage in the process of DNA metabolism, but this means that they also limit the possibility of DNA repair when this damage is done [37]. The most important protein from this group is the telomeric repeat–binding factor (TRF2) [38]. When the telomere length is significantly reduced and when they reach the so-called “critical length”, double-strand breaks occur. This triggers the DNA-damage response (DDR) [39]. As we will see later, this process is most responsible for the initiation and maintenance of senescence [8,39]. It is still not known what is the exact threshold of telomere length or the number of dysfunctional telomeres required to induce senescence [6]. A cell is considered senescent when its telomeres have reached a critical length, and given that DNA damage can only be repaired if the cells have the possibility of reproduction; when permanent cell cycle arrest occurs, the possibility of repairing the damage is lost [36].

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