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PATHOLOGICAL MORPHO-FUNCTIONAL DYSINTEGRATION AS THE KEY PATHOGENETIC MECHANISM OF EXPERIMENATL LIVER CIRRHOSIS

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The purpose of the study is to investigate the liver cirrhosis pathophysiological mechanisms in rats and to investigate the efficacy of pathogenetical correction of these pathology using L–arginine aspartate and tivortin. Experimental studies proved the lipid peroxidation involvement into the liver cirrhosis pathogenetic mechanisms. The data obtained indicate the cellular apparatus of the blood participation in the pathogenetic mechanisms of the hepatocytes lesions. The data received in morphological studies are comparable with the results of biochemical investigations confirming the unified concept of pathological morpho-functional disintegration development in conditions of investigated pathology that is the basis for the multiple organ failure syndrome development. The authors argue that the positive results of both L–arginine aspartate and tivortin using in experimental liver cirrhosis are supposed to be an experimental background of these pharmacons clinical efficacy testing.

Key words: experimental liver cirrhosis, lipid peroxidation, morphological disturbances, pathophysiological mechanisms, L–arginine aspartate, tivortin, pathological morpho–functional dysintegration

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Treatment of patients with liver cirrhosis (LC) and its complications is one of the most difficult problems of surgery, in particular, surgical hepatology and biliary surgery [10, 6]. According to the WHO, the frequency of LC is steadily increasing [12, 14]. According to the results of pathological studies this data differs from 1 to 11% [9, 15]. High LC incidence is due to increased incidence of acute viral hepatitis, especially, type B, C, D, resulting in the hepatic parenchymal inflammatory-destructive process transformation into chronic [2, 3, 8] with LC formation and other complications development [11]. Liver cirrhosis is accompanied by high mortality, entering, according to the WHO, up to 10 diseases with the highest mortality [7].

To investigate the hepatic morpho–functional changes we created an experimental model of LC. The blood serum and erythrocytes, hepatic and pancreatic parenchyma oxidative-antioxidant homeostasis activity as well as structural changes in liver in conditions of LC were studied. Taking into account systemic disorders in patients with LC the rate of hepatocellular insufficiency progression, as well as the frequent occurrence of multiorgan failure syndrome with pancreatic, gallbladder, stomach lesions and vascular component in this disease involvement into the pathologic process we suspected the influence of one of the typical pathological processes – inflammation – in the pathogenesis of these disease. Lipoperoxidation activation is one of the body's response manifestations to the alterative factors action that initiate a systemic inflammatory response.

The purpose of the study is to investigate the LC pathophysiological mechanisms in rats and to investigate the efficacy of pathogenetical correction of these pathology using L–arginine aspartate and tivortin.

Materials and methods. The experiments were performed under conditions of chronic experiment on 180 male rats lines Wistar adult (over 6 months), body weight of (200±20) g, kept in conventional vivarium conditions. Using random sampling, the animals were divided into following groups: 1 group – animals without simulated pathology (intact, n=10), which via a plastic probe were intragastrically injected 4 ml of solvent (refined sunflower oil); group 2 – animals with simulated LC (n=80), which is a pathological condition was reproduced by introducing hepatotropic poison – carbon tetrachloride, which produces a direct cytolytic effect on the liver parenchyma. A solution was prepared from pure (99.99 %) of the drug by the addition of refined sunflower oil in the ratio 1:1 and was administered intragastrically using a plastic probe twice a week (Monday and Thursday) in a volume of 4 ml for 10 weeks. Control of the formation of experimental liver cirrhosis was carried out by diagnostic laparotomy with biopsy and subsequent histological examination of the biopsy specimens; 3 group – rats (n=45) in which LC was modeled and L–Arginine aspartate was performed (50 mg/kg, intraperitoneally [i.p.] daily during the whole period of investigation; group 4 – rats (n=45) in which LC was modeled and pharmacological correction using tivortin (100 mg/kg, i.p.) was carried out once daily during the whole period of investigation with biopsy and subsequent histological examination of the biopsy specimens.

During the period of experience 21 animals died from acute liver failure, which was 26.3 % of the total number of animals that modeled LC. Left 59 rats which after 12 h, 1, 3, 5 and 7 days after completing the simulation of the LC were taken from experiment by Thiopental sodium (100 mg/kg, i.p.) oberdose. After euthanasia the blood and internal organs of rats were sent for biochemical study.

In a separate series of studies, after LC simulation in 90 rats euthanasia was performed after 1, 6, 12 h, 1, 3, 5 and 7 days. Blood was taken from animals (each group in a certain period of time consisted out of 6 rats) [8] and the concentration of intermediate products of lipid peroxidation – Malondialdehyde (MDA), Conjugated Dienes (CD) – and activity of antioxidant enzymes – Superoxidedismutase (SOD), Glutathioneperoxidase, Glutathionereductase – was determined by standard methods.

After euthanasia, the liver and pancreas were taken from all animals, tissue samples were homogenized in the environment of 10 mmol Tris–HCl buffer (pH=7,4) at a ratio of 1:9. To obtain a solid fraction, the homogenate was centrifuged for 10 min at a speed of 3000 g (t = 0–2 ^{0}C). Supernatant was used to determine the concentration of MDA, CD and the activity of antioxidant enzymes – SOD, Glutathione peroxidase and Glutathione reductase. The intermediate products of lipoperoxidation concentration were determined by standard methods. SOD activity was determined by the level of inhibition of Nitro blue tetrazolium recovery in the presence of Nicotinamide adenine dinucleotide (NADH) and Phenazine methosulfate; the activity of Glutathione peroxidase – by the velocity of oxidation of glutathione in the presence of tert-Butyl hydroperoxide; the activity of Nicotinamide adenine dinucleotide phosphate (NADPH) – Glutathionereductase – by the velocity of recovery oxygenated Glutathione in the presence NADPH, the concentration of total Glutathione - by the method described in work [5], the content of α-tocopherol - by the method [5].

To implement histological study the tissue material was fixed in 10 % solution of neutral buffered formalin. Further histological preparations were performed according to standard techniques [1]. Production of serial paraffin sections with a thickness of 4–6 µm were carried out on the sliding microtome. Staining preparations were made with hematoxilin and eosin.

For document images of histological preparations were taken on the computer monitor using the Delta Optical microscope and digital camera (Digital Camera SCMOS) using software ToupWiew at different magnifications.

Biochemical and morphological studies were performed in rats with LC, as well as rats were administered L–Arginine aspartate (50 mg/kg, i.p.) and tivortin (100 mg/kg, i.p.) for medicinal purposes which are characterized by antiinflammatory (due to their antioxidant, membrane stabilizing, energy saving and other effects) and hepatoprotective properties.

The results were processed statistically using one-way ANOVA parametric criteria. $p<0.05$ was chosen as the minimal criteria of reliability.

Results of the study and their discussion. In the study of the liver structure in animals with experimental LC it was found that the structure of hepatic lobules was impaired. Central veins were well visualized, their lumens were slightly expanded, contained a small amount of red blood cells. In most cases, the lumens of sinusoidal capillaries were not detected, or were revealed only in centrolobular position. Organization of hepatic lamina was impaired in whole lobule. The cytoplasm of hepatocytes located in centrolobular zone, the middle third of the lobule and periportally fields were changed, and the vast majority of hepatocytes were light and empty, which is the sign of ballooning degeneration. The majority of hepatocytes contained nuclei, however, they are both visually and morphometrically decreased and shrinked.

In individual cells on the background of destructive changes of the cytoplasm nuclei were with signs of caryopycnosis and caryolysis, indicating the presence of dystrophic-necrotic manifestations. The contours of the cells changed dramatically, the vast majority increased, deformed, cell-to-cell junctions were damaged. Portal tracts expanded mainly due to the expansion and plethora of vessels, mucoid and fibrinoid swelling of blood vessels walls, perivascular edema and lymphoplasmacytic infiltration, the formation of septal sclerosis (fig. 1), a minor expansion of the bile duct without visualization of bile pigments.

Histological examination of the liver of animals with a simulated LC in the correction by L–Arginine aspartate it was found that partial structure of the liver parenchyma was significantly restored. Central veins were well visualized, with their lumnes slightly expanded, remained moderately plethoric. Their lumens were detected signs of venous congestion. Sinusoidal capillaries are moderately expanded. Organization of hepatic lamina were restored in whole lobule. The cytoplasm of the cells was structured. The vast majority of hepatocytes contained nuclei, the relative amount of damaged cells was decreased. Cell–to–cell junctions in the vast majority of cells were recovered.

The regenerative activity of the tissues visually increased. Portal tracts remained expanded, mainly due to the expansion and plethora of blood vessels, a slight expansion of the bile ducts, moderate lymphohistiocytic perivascular infiltration with marked stromal collagenization. Perivascular edema remained minor (fig. 2).

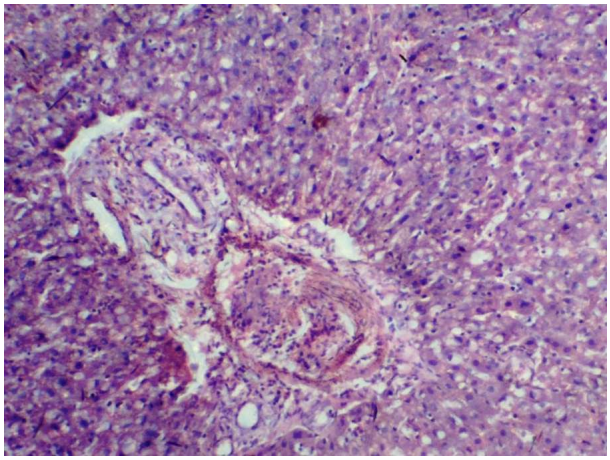

Fig. 1. The structure of the liver of animals with simulated LC. A significant expansion of portal tracts with the formation of septal sclerosis, perivascular edema and lymphoplasmacytic infiltration. Dystrophic changes in hepatocytes. Staining with hematoxilin and eosin. ×100.

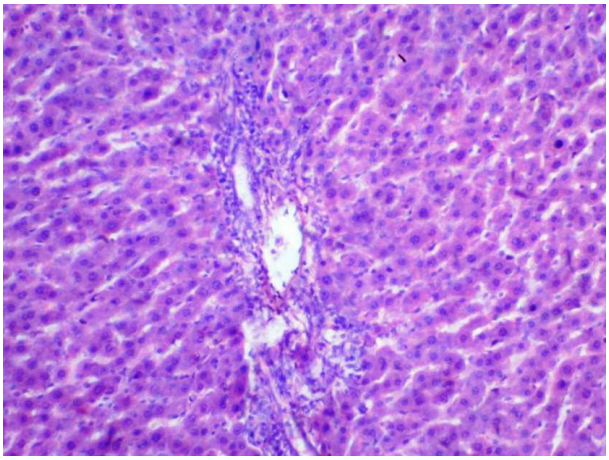

Fig. 2. The structure of the liver of animals with LC using L–Arginine Aspartate for the pharmacological correction. Expansion of portal tracts mainly due to the expansion of blood vessels and lymphoplasmacytic infiltration. Reduction of dystrophic changes in hepatocytes. Staining with hematoxilin and eosin. ×100.

In animals with experimental LC after the introduction of Tivortin, the same with the introduction of L–Arginine aspartate, but more pronounced, normalization of the liver morphological structure and intraorganic vascular network was observed.

In the blood of rats with experimental LC significant accumulation of MDA and CD was noted, the absolute concentration of these substances after 12 hours of the experience was, respectively, 2.69±0.18 nmol/l and 0.70±0.07 µmol/l, which is 1.9 times ($p<0.001$) and 1.7 times ($p<0.01$) exceeded the relevant figures in the control group (table 1).

Table 1

Concentrations of lipoperoxidative products and activity of antioxidant enzymes in blood of rats at different times after the LC simulation

Index	Control group (n=9)	The value of an index at the time of observation (M±m)				
		12 hours	1 day	3 days	5 days	7 days
MDA, nmol/l	1,41±0,11	2,69±0,18***	3,77±0,29***	4,41±0,37***	3,86±0,26***	2,27±0,23**
CD, µmol/l	0,41±0,05	0,70±0,07**	0,86±0,08***	0,97±0,11***	0,84±0,07**	0,67±0,06*
Catalase, i.u.	1,92±0,13	1,31±0.13**	1,18±0,12***	1,08±0,10***	1,21±0,11**	1,49±0,14*
SOD, U/ml	2,79±0,17	1,68±0,16**	1,56±0,14***	1,48±0,13***	1,62±0,17**	1,97±0,20*
Total gluta-thione, µmol	20,1±0,6	15,7±1,1*	15,1±1,0**	14,4±1,2**	15,6±1,3*	16,6±1,3
α–tocopherol, µmol /ml	51,8±3,7	38,9±3,8*	35,9±3,5**	33,4±3,3**	36,2±3,7*	37,3±3,6*

Notes: The difference of indexes compared to those in the control group are statistically reliable: * $p<0.05$, ** – $p<0.01$, * * * $p<0.001$ (one-way ANOVA criteria).

In the future, the levels of MDA and CD continued to increase, reaching on the third day of the pathological process, when the value of indices in 3.1 times and 2.4 times higher than in control ($p<0.001$). Further, a slight decrease in the level of MDA and CD was found, however, on the seventh day it exceeded that in control ($p<0.05$).

Under these conditions in the blood of rats a significant decrease in the activity of antioxidant enzymes – catalase, SOD, Glutathione, α–tocopherol was observed, which was the minimum for 3 days after LC simulate ($p<0.01$). The activity of the enzymes has not recovered to the 7-day experiment ($p<0.05$).

The concentration of liporexidation intermediate products in erythrocytes in the 1^{st} – 5^{th} day of LC was the same, maximal MDA and CD concentration was registered on the 3^{rd} day when these indexes were 2,5 times ($p<0.001$) higher pertaining the same in the control group. The activity of catalase, SOD, Glutathioneperoxidase and Glutathionereductase were maximally reduced on the 3^{rd} day of LC ($p<0.05$).

In the LC rat's liver tissue it was observed that a significant increase in the level of MDA and CD, which is already in 12 hours after simulate of the pathological process, respectively, on 85 and 129 % was higher than in the control group ($p<0.001$, Table 2). The maximum marked accumulation of intermediate

lipoperoxidative products was observed in the first day ($p<0.001$) with a slight decrease in the indices on the 3rd ($p<0.001$) and 5th ($p<0.05$) days of the trial. On the 7th day the indices were not different in the main and control groups ($p>0.05$). The course of the pathological process is also characterized by a pronounced ($p<0.05$) decrease of the activity of antioxidant enzymes, which lasted to the 5th day of experiment (table 2).

Table 2

Concentrations of lipoperoxidative products and activity of antioxidant enzymes in liver parenchyma of rats at different after the LC simulation

Index	Control group (n=9)	The value of an index at the time of observation (M±m)				
		12 hours	1 day	3 days	5 days	7 days
MDA, µmol/g	2,82±0,23	5,21±0,41***	6,43±0,51***	5,49±0,42***	4,87±0,31***	2,82±0,23
CD, µmol/g	0,41±0,06	0,94±0,09***	1,12±0,10***	1,06±0,10***	0,88±0,08*	0,41±0,06
SOD, U/g	1,86±0,17	1,07±0,07**	1,03±0,07***	1,00±0,06***	1,14±0,09*	1,86±0,17
Glutathione peroxidase, U/g	2,56±0,21	1,34±0,13**	1,21±0,11***	1,29±0,11**	1,49±0,12*	2,56±0,21
Glutathione reductase, U/g	2,66±0,13	1,62±0,14**	1,32±0,11***	1,41±0,12***	1,78±0,14*	2,66±0,13

Notes: The difference of indexes compared to those in the control group are statistically reliable: * $p<0.05$, ** – $p<0.01$, * * * $p<0.001$ (one-way ANOVA criteria).

Similar changes, in particular, the decrease of the activity was noted about antioxidant enzymes in pancreatic parenchyma – SOD, Glutathione peroxidase and Glutathione reductase ($p<0.05$). The course of LC under these conditions was accompanied by a significant ($p<0.05$) increase of the level of MDA and CD, and decrease of the activity of antioxidant enzymes in the parenchyma of the pancreas.

Pharmacological correction of experimental LC using L–Arginine aspartate and Tivortin was a significant decrease of the concentration of intermediate lipoperoxidayive products and activation under the influence of the applied compounds with enzymatic antiradical activity.

The results after critical analysis allow to formulate the following basic provisions relating to the pathophysiological mechanisms of experimental LC. Firstly, LC is accompanied by increased activity of lipid peroxidation processes, which is manifested by accumulation of intermediate lipoperoxidative products and decreased activity of enzymatic and non-enzymatic branches of the system of antioxidant protection. These facts are negotiated with the opinion of prominent experts [3, 4, 10] about the pathogenetic role of intensification of lipid peroxidation process in some pathological processes, in particular, inflammation, high temperatures, radiation factors, other damaging influences.

The data indicate the participation of the blood cellular apparatus, namely red blood cells, in the pathogenetic mechanisms of hepatocytes death, because in the erythrocytes the data were unidirectional with those in the blood plasma. i.e. the increase in the concentration of lipoperoxidative products and a decrease in the activity of antioxidant enzymes. Summarizing these results and suggestions one could suppose the generalization of the pathological process with LC which explains how the speed of his progression and spread of abnormal changes in the cells that should be taken into account in the clinical conditions in determining the tactics of patients treatment [2, 14].

We identified the associated processes of lipid peroxidation intensification and the antioxidant defense system inhibition occurring directly in the tissues of the liver. These data explain the speed of disease progression, high volume and typically of irreversibility of the pathological process of cells destruction in case of LC [7, 14]. According to anatomic unity, common physiological functioning and similar to those in liver parenchyma disorders which were manifested by the shift of the dynamic equilibrium in the system "lipid peroxidation – the antioxidant system" in the direction of the intensification of processes of lipid peroxidation, it was clearly demonstrated somewhat less pronounced than in the liver tissue, lipoperoxidative products accumulation and antioxidant defense system inhibition in the pancreatic parenchyma.

Comparable to the results of biochemical research are the data of morphological studies, which confirm a unified concept of the formation of pathological morpho–functional disintegration in conditions of formed pathology [3]. Analyzing the data become apparent pathophysiological mechanisms of multiple organ failure syndrome with LC, hepatic fibrosis, portal hypertension, liver failure. Given the morphological disorders and the intensification of lipid peroxidation processes and the associated inhibition of the activity of antiradical protection, important in terms of planning schemes of LC complex pathogenetically treatment is the inclusion of drugs with antioxidant properties that will help reduce the severity of hepatocytes destruction to prevent liver failure.

We consider, useful in the future, further implementation of our research results, which indicate a normalizing effect of L–Arginine aspartate and Tivortin on morpho–functional activity in experimental LC. Their hepatoprotective activity was similar in severity with a slight predominance of that of L–Arginine Aspartate and manifested, beginning with the 6th hour after LC was simulated.

Conclusions

1. The LC manifestation is accompanied by lipid peroxidation processes activation in the blood, erythrocytes, liver parenchyma and the pancreas which is accompanied by intermediate lipoperoxidative products accumulation and both antioxidant system enzymatic and non-enzymatic branches activity inhibition.

2. Such way of pathological process manifestation explains the speed of his progression, high expansion and irreversible destruction of cells with LC that from fundamental view demonstrates the unity of pathogenetic mechanisms of damage of the liver parenchyma under conditions of the studied pathology, reflects the systemic inflammation in LC, highlights the formation of pathological morpho–functional disintegration, which is the basis for the development of multiple organ failure syndrome.

3. L–Arginine aspartate and Tivortin administration in experimental LC contributes to lipid peroxidation processes suppression in blood, erythrocytes and in both hepatic and pancreatic parenchyma and normalizes the functioning of liver cells. Therefore one should suppose these data as the experimental background of these pharmacons clinical efficacy testing.

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Реферати

ПАТОЛОГІЧНА МОРФО-ФУНКЦІОНАЛЬНА ДЕЗІНТЕГРАЦІЯ ЯК ПРОВІДНИЙ ПАТОГЕНЕТИЧНИЙ МЕХАНІЗМ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ЦИРОЗІ ПЕЧІНКИ

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Мета дослідження - вивчення патофізіологічних механізмів цирозу печінки у щурів та дослідження ефективності патогенетичної корекції цієї патології застосуванням L–аргініну аспартату та тивортину. Проведені експериментальні дослідження підтвердили залучення процесів ліпопероксидації до патогенетичних механізмів цирозу печінки. Результати свідчать про участь клітинного апарату крові в патогенетичних механізмах загибелі гепатоцитів. Співставними з результатами біохімічних досліджень є дані морфологічних досліджень, які підтверджують єдину концепцію формування патологічної морфо-функціональної дезінтеграції за умов сформованої патології, що є підставою розвитку синдрому

ПАТОЛОГИЧЕСКАЯ МОРФО-ФУНКЦИОНАЛЬНАЯ ДЕЗИНТЕГРАЦИЯ КАК ВЕДУЩИЙ ПАТОГЕНЕТИЧЕСКИЙ МЕХАНИЗМ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ ЦИРРОЗЕ ПЕЧЕНИ

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Цель исследования - изучение патофизиологических механизмов цирроза печени у крыс и исследование эффективности патогенетической коррекции данной патологии применением L–аргинина аспартата и тивортина. Проведенные экспериментальные исследования подтвердили вовлечение процессов липопероксидации в патогенетические механизмы цирроза печени. Результаты свидетельствуют об участии клеточного аппарата крови в патогенетических механизмах гибели гепатоцитов. Сопоставимыми с результатами биохимических исследований являются данные морфологических исследований, подтверждающие единую концепцию формирования патологической морфо-функциональной дезинтеграции в условиях воспроизводимой патологии, что является основой развития синдрома

поліорганної недостатності. Автори стверджують, що позитивні результати застосування L–аргініну аспартату та тивортину за умов експериментального цирозу печінки є експериментальним обгрунтуванням доцільності тестування клінічних ефектів вказаних лікарських сполук.

Ключові слова: експериментальний цироз печінки, перекисне окислення ліпідів, морфологічні порушення, патофізіологічні механізми, L–аргініну аспартат, тивортин, патологічна морфо–функціональна дезінтеграція

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полиорганной недостаточности. Авторы утверждают, что положительные результаты применения L–аргинина аспартата и тивортина при экспериментальном циррозе печени является экспериментальным обоснованием целесообразности тестирования клинических эффектов указанных лекарственных препаратов.

Ключевые слова: экспериментальный цирроз печени, перекисное окисление липидов, морфологические нарушения, патофизиологические механизмы, L–аргинина аспартат, тивортин, патологическая морфо–функциональная дезинтеграция

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DYNAMICS OF ATP-POSITIVE DENDRITIC CELLS IN RAT'S OROPHARYNGEAL SUBMUCOSA AFTER ANTENATAL ANTIGEN ADMINISTRATION

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Purpose of the work was to establish dynamics and morphology of DCs, located in oropharyngeal submucosa the postnatal period after antenatal antigen effect on a fetus. DCs were detected on the cryostat sections of the pharynx tissue by using the Vakhshtein-Meizel method. In experimental newborns, the DCs absolute number was found to be greater than in the control and did not change during the first week, unlike in the control, where this index did not change significantly over the two weeks of life. All groups of animals have been increased DCs absolute number by third week of life, while the antigen load on the body increases. Experimental animals, regardless of the antigen administration mode, have been taken place DCs activation earlier than in control, that is, at 7th life day. Animals which underwent antenatal antigen administration during fetal period has been increased number of their processes compared to control. Although it was founded that DCs in experimental groups are stained more shade than in control group, which indicating a more active ATP accumulation.

Key words: ATP, antenatal antigen administration, dendritic cell, pharynx, local immunity.

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Dendritic cells (DCs) form a widely distributed cellular net throughout the body. DCs not only exert immune-surveillance for antigens of different origin, but also later activates naive T lymphocytes by giving rise to various immunological responses [2]. The immune complex of oral cavity and pharynx (as a part of a MALT – Mucosa Associated Immune Tissue) might represent the deserve immunological challenges continuously faced by its mucosa. DCs take a crucial part in linking innate and adaptive immunity, either as in mediating immunity or tolerance. Mucosa associated DCs, especially of oral mucosa, should be thoroughly studied in our attempt to understand formation oral immunity. Besides, it is not always possible to extrapolate oral DCs function from their counterparts in non-oral tissues [7]. Also mucus form a nonspecific physical barrier and constrains the immunogenicity of antigens by delivering tolerogenic signals [13].

It is proved that antigen-presenting cells play a central role in transferring information from the periphery of the organism to lymphoid organs. They deliver important signals which result in T cell unresponsiveness with antigen-specific tolerance induction. The initiation of effector $CD8^+$ T-cell responses needs the presentation of peptide bond derived from internalized antigen on class I major histocompatibility complex molecules by DCs in a process called cross-presentation [4].

Antigen load on body, especially on barrier mucosa, can be materialize not only bacteria and viruses but artificially by vaccination, or by antenatal antigen administration on fetus in case mother has undergone some infection during pregnancy [5]. According to Apostolopulose's opinion, a major aim in vaccine development is to induce powerful, specific T-cell responses [1]. This is achieved by targeting antigen to cell surface molecules on DCs that begins receptor mediated endocytosis for loading onto MHC molecules and stimulation of T-cell responses.

It is known, that type III interferon (IFN-λ) is important for innate immune protection at mucosal surfaces and has therapeutic benefit against influenza A virus infection (IAV). According to Hemann's opinion, IFN-λ signaling in DCs populations was critical for the development of protective IAV-specific $CD8^+$T cell responses. It is proofed that mice lacking the IFN-λ receptor had decreased $CD8^+$ T cell