Analysis of apoptotic markers Fas/FasL (CD95/CD95L) expression on the lymphocytes in patients with acute coronary syndrome

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Abstract

Background: Acute coronary syndromes are caused by the rupture or erosion of an atherosclerotic plaque which by secreting a variety of proteases is capable of degrading pericellular matrix components induces death of endothelial cells. This mechanism plays the main role in apoptosis.

Aim: To estimate expression of apoptotic Fas/FasL (CD95/CD95L) on lymphocytes in the peripheral blood.

Methods: We examined patients with acute myocardial infarction (n=18, mean age 62±8 years), in unstable angina pectoris (n=31, mean age 62±10 years) and in a control group (n=20, mean age 62±9 years) without coronary risk factors and inflammatory condition. All investigations of Fas/FasL were performed by flow cytometry. Inflammatory parameters and standard risk factors were investigated by standard methods (ELISA).

Results: The analysis revealed a higher expression of Fas and FasL molecules on the lymphocytes from patients with acute myocardial infarction ($p < 0.001$, $p < 0.002$) and unstable angina ($p < 0.01$, $p < 0.02$) compared to the control group. Moreover we found a statistically significant positive correlation between the level of LDL cholesterol and hypertension and prevalance of CD95 ($p < 0.001$, $p < 0.01$) and CD95L ($p < 0.02$, $p < 0.03$) in patients with acute myocardial infarction.

Conclusions: A higher expression of apoptotic molecules (Fas and FasL) on lymphocytes occurs before the onset of acute ischaemia and contributes to the plaque rupture and acute coronary syndrome. Furthermore, antiapoptotic therapy leads to plaque stabilisation.

Key words: myocardial infarction, unstable angina, apoptosis

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Introduction

Apoptosis is one of the forms of programmed cell death, also called physiological death, and is a control mechanism that enables excessive and useless cells to be removed at a proper time. It plays a key role in many acute conditions, such as sepsis, SIRS, acute liver failure, myocardial infarction (MI), and chronic diseases such as Parkinson's and Huntington's disease, rheumatoid arthritis and autoimmunological disorders (Graves--Basedov disease, Hashimoto type thyroiditis) [1].

Apoptosis abnormalities may contribute to the development of inflammation within atherosclerotic plaque leading to its ulceration or rupture, and eventually to the occurrence of acute coronary syndrome. There is a fundamental difference between endothelial cell and macrophage/monocyte apoptosis. In the case of endothelial cells, their death leads to atherosclerosis progression and atherosclerotic lesion rupture [2]. Conversely, inflammatory cell apoptosis (macrophages/monocytes) stabilises atherosclerotic plaque [3]. Acute coronary syndrome (ACS) is a clinical manifestation of processes involving rupture of atherosclerotic lesion combined with thrombus formation on its surface. These transformations are associated with local accumulation of

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several molecules (such as cytokines, adhesive molecules), ongoing inflammatory process, oxidative stress, endothelial cell or macrophage apoptosis and necrosis. Inflammation and oxidative stress stimulate macrophages to produce metalloproteinases (MMP) that degrade extracellular matrix proteins and cause fibrin breakdown [4].

The process of apoptosis is controlled by apoptotic proteins that are expressed on the lymphocytes isolated from the infarcted area of the myocardium. Activation of the complex Fas/FasL (transmembrane superfamily TNFR proteins) plays a key role that initiates the intracellular transformation cascade. The cytoplasmic part of the activated Fas receptor binds adaptive protein, e.g. FADD (fas-associated death domain protein). The formed Fas-FADD complex activates caspase-8, which initiates some cystein proteases of caspase-3 which are considered effector agents in apoptosis [5]. This cycle of processes is important in elimination of the peripheral T lymphocytes, inflammatory and neoplastic cells, which is mediated by cytotoxic cells such as CD8 and NK. Meanwhile, molecules that inhibit apoptotic signals include FAP-1 (Fas associated phophatase-1), inhibiting signal transfer from Fas on the regulatory domains as well as FLIP, preventing formation of complex Fas-FADD-FLICE, also called a complex of adaptative proteins, that is a further stage of physiological cell death. In its final phase, a cycle of caspases transformation takes place and regulators limiting programmed cell death are inhibitory apoptotic proteins (IAB) and Bcl-2 molecule. The latter is one of the regulatory proteins of apoptosis (Bcl-2 family members) that confines either anti-apoptotic molecules (Bcl-2, BAG-1) or pro-apoptotic ones, such as Bax type [6]. Both types of molecules may be present on the endothelial cells and lymphocytes within atherosclerotic plaque [7].

Undoubtedly, apoptosis of the endothelial cells may initiate erosion of the atherosclerotic lesion followed by thrombus formation that may finally lead to ACS and progressive loss of cardiomyocytes. Death of cardiomyocytes results eventually in heart failure. Most studies on animal models and most recently also on 'the human heart' showed that progressive postinfarction myocardial dysfunction was caused by loss of vital cardiomyocytes. Apoptosis of these cells within the ischaemic area underlies postinfarction pathophysiology of heart failure [8].

The aim of our study was to answer the following questions:

1. Is there any expression of apoptotic markers in the ACS patients such as those with MI or unstable angina?
2. Does expression of the examined apoptotic proteins (Fas, FasL) correlate with the classical risk factors?
3. What is the contribution of the apoptotic proteins to the pathophysiology of ACS?

Methods

Study group

The study involved 48 adult patients with acute MI (n=18, mean age 60±8 years) and unstable angina (n=31, mean age 62±10 years) admitted to our department between 2000 and 2003 and treated in the Outpatient Cardiac Clinic. Myocardial infarction (group A) was diagnosed based on clinical presentation, elevated levels of myocardial necrosis markers and changes in ECG (both STEMI and NSTEMI). Unstable angina (UA) was detected if no release of biomarkers (troponin I and CK-MB) was noted. Patients with acute infections, serious liver and renal disorders, diabetes mellitus, severe valvular heart disease, cardiomyopathies and chronic non-cardiac disorders (e.g. cancers) that might have significantly altered impacted the actual inflammatory status were excluded from the study. All examined patients received acetylsalicylic acid, beta-blockers, angiotensin-converting enzyme inhibitors and statins. The control group consisted of 20 apparently healthy blood donors aged 44 to 71 years without evident atherosclerosis risk factors.

Standard assessment

In the examined groups of patients the following parameters were assessed: body mass index (BMI), acute phase reaction parameters (leucocytosis, C-reactive protein, fibrinogen) and typical risk factors of atherosclerosis such as positive familiar history, hypertension, elevated levels of lipid fractions (total cholesterol >90 mg/dl, LDL-cholesterol >100 mg/dl, HDL-cholesterol <40 mg/dl and triglycerides >150 mg/dl) as well as smoking (smokers of more than 10 cigarettes a day).

The blood samples for evaluation of acute phase reaction parameters, glucose and lipid metabolism and markers of myocardial necrosis were drawn to the plastic tubes without any anticoagulants and directly processed. A latex test (Humatex CRP) was used to measure C-reactive protein (CRP) concentration and Multibren U test for fibrinogen. Body mass index (BMI) was calculated according to the formula: weight (kg)/height^2 (cm). Lipid parameters (total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol) were assessed by means of enzymatic methods.

Test for apoptotic proteins

To assess apoptotic proteins, 2 cm^3 of blood for EDTA was collected, then blood samples were

Table I. Clinical characteristics of the examined patients

Parameter	Acute myocardial infarction	Unstable angina	Control group	p and p*
	n=18	n=31	n=20	
Age [years]	57.83±6.0	58.83±8.0	56±9.5	NS, NS*
Gender (males/females)	15/3	23/8	11/9	
BMI [kg/m^2]	28.8±2	28.3±3	25.3±1.3	p <0.0001, p* <0.0001
Positive family history [%]	100	93.5	0	0
Smoking [%]	50	48.3	0	0
Hypercholesterolemia [%]	88.8	93.5	0	p <0.001, p* <0.002
Hypertension [%]	83.3	70.9	0	p <0.0001, p* <0.002
Leucocytosis [1/µl]	7866.6±1929	6519.1±2052	4911±857	p <0.0001, p* <0.001
CRP	13.38±2.6	8.77±2.8	5.68±1.1	p <0.0001, p* <0.0001
Fibrynogen	381.2±103	331.4±101.07	267±85	p <0.0001, p* <0.0001
CKMB (U/l)	57±16	16±9	10±5	p <0.001, p* <0.01
Troponin T (ng/ml)	0.24±0.6	<0.03	<0.03	p <0.01, p* <0.01

p – differences between MI and control group, p – statistical significance of differences between UA and control group*

centrifuged (2000 rates/min for 10 minutes) and finally prepared for cytometric analysis. A 10 µl of each of two- or three-colour stained (FITC – fluorescein isothiocyanate, PE – phycoerythrin, PerCP – peridinin chlorophyll protein) monoclonal antibodies (Becton Dickinson: CD3-FITC/CD95-PE, CD3-PerCP/CD95L-FITC) were added to the samples of 100 µl of the whole blood. After a 15-minute incubation at room temperature each sample underwent a process of rapid lysis according to a procedure of adding the following sequence of chemical agents: formic acid causing erythrocyte lysis, sodium carbonate as leucocyte membrane stabiliser, and paraformaldehyde as fixing agent. After careful automatic mixing, each sample was analysed using the flow cytometer (Coulter EPICS XL). Each time, 10^4 cells were assessed.

Statistical analysis

The results were analysed by means of mean arithmetic, median (Med) and standard deviation (SD) or percentage for each parameter. Statistical significance of differences between consecutive values were evaluated using Student's t-test confirmed by non-parametric Mann-Whitney U test. Differences with p value <0.05 were considered significant. Pearson-Spearman linear correlation index was used to assess the correlation power between investigated parameters.

Results

Clinical characteristics of the examined patients are presented in Table I. Significantly higher values of the analysed acute phase reaction parameters such as CRP, fibrinogen and leucocyte counts were noted in patients with both acute MI and UA in comparison with the control group. Regarding BMI, a significant difference was also seen between the group of patients with either MI or UA and the control group. Mean cholesterol concentrations in patients with acute MI (215.12± ±46 mg/dl) and UA (192.67±67 mg/dl) were significantly higher than in the control group (151.8±15 mg/dl). Similarly, mean values of arterial pressure in the examined group were markedly higher than in the control group (p <0.001).

Analysis of pro-apoptotic molecules expression showed a significant increase in both Fas/CD95 and FasL/CD95L expression on lymphocytes isolated from patients with acute MI (Figure 1a) and UA (Figure 1b) in comparison with the control group (Figure 2).

In patients with acute MI, significant positive correlations between either LDL-cholesterol concentration or arterial pressure value and percentage of CD3 lymphocytes with Fas expression (CD 95) and FasL (CD 95L) were noted (Table II).

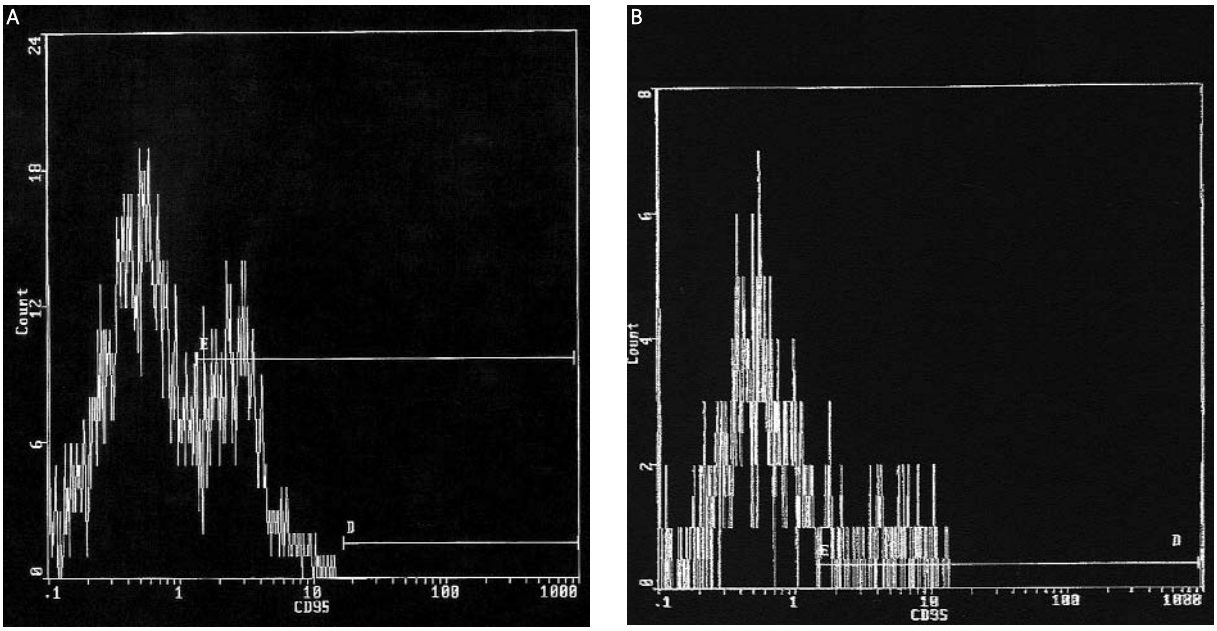

Figure 1. Fas molecule (CD95) expression on the surface of peripheral blood lymphocytes in patients with acute MI (%CD3-Fas$^+$ 70%) and UA (%CD3-Fas$^+$ 45%)

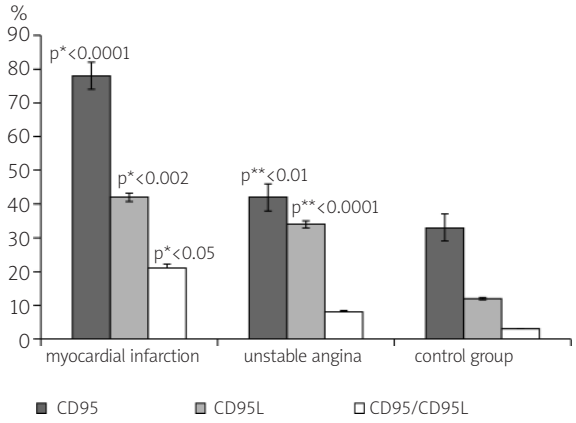

Figure 2. Expression analysis of CD95/CD95L apoptotic molecules on the surface of the peripheral blood lymphocytes in patients with acute MI, UA and the control group
** between MI and controls*
*** between UA and controls*

Table II. Correlations between apoptotic molecules and LDL-cholesterol concentration or arterial pressure value in patients with acute MI

Correlations	Fas (CD95)	FasL (CD95L)
LDL-cholesterol	R=0.48, p <0.001	R=0.72, p <0.02
Systolic blood pressure	R=0.54, p <0.01	R=0.28, p <0.03

Discussion

The results of previous studies showed that atherosclerotic plaque was composed of accumulated smooth muscle cells, collagen and fibrin as well as circulating lipids and migrating inflammatory cells (e.g. lymphocytes, macrophages and endothelial cells). These cells through a release of pro-inflammatory cytokines such as TNF-α, INF-γ, TF, IL-1β, IL-6 and IL-8 participate in destabilisation of the atherosclerotic lesion and eventually lead to the occurrence of ACS [9].

In the study presented herein, expression of pro-apoptotic molecules in acute MI and UA was evaluated. The analysis confirmed increased expression of Fas and FasL molecules on the lymphocytes' surface in the examined group of patients when compared to the control group.

Aforementioned markers are proteins that may induce apoptosis of cardiomyocytes, and Fas is a crucial marker of MI dependent from ischaemia/reperfusion processes in vivo [10]. Earlier studies involving patients with diagnosed ACS with ST-segment elevation (STEMI-ACS) performed up to six hours after onset of chest pain showed the increased concentrations of such markers as Fas and FasL and subpopulation of T lymphocytes, surface HLA DR+, expression of CD 69+ in comparison with their concentration in patients with stable coronary artery disease. Activation of these parameters takes place prior to the beginning of ischaemia and contributes to atherosclerotic plaque rupture as well as progression of myocardial

necrosis [11]. In the experimental studies, increased expression of Fas and FasL on mice inflammatory cells was noted, indicating pronounced apoptosis within the area surrounding the necrotic myocardium when compared to the control group [12]. In our study, increased expression of the molecules was observed up to the 12th hour of the ACS course. According to the experiments on rats, expression of pro-apoptotic Bac and Fas increases at the 12th hour of acute MI and reaches its peak at the 24th hour for Bax but at 72nd for Fas, and is associated with the area surrounding the ischaemic myocardium and AG II expression [13]. In the available literature, decreased expression of anti--apoptotic Bcl-2 molecule was observed in a group of patients with acute MI. Our results are consistent with the experimental studies on animals that revealed a favourable impact of vector with Bcl-xL administered up to the 4th day of acute ischaemia in acute MI, preventing adverse remodelling of the left ventricle by inhibition of apoptosis and opening new therapeutic cardioprotective perspectives for Bcl-xL [14].

All our study patients with ACS received therapy including angiotensin-converting enzyme inhibitors and beta-blockers. Previous experiments in rats showed a favourable impact of therapy with beta-blocker (carvediol) on cardiomyocyte apoptosis in acute MI through increased Bcl-2 expression [15]. Similar results regarding an influence of metoprolol and atenolol were shown by Chinese investigators [16]. Such a therapy increased survival after MI and prevented progressive left ventricular dilatation and dysfunction.

We found a significant relationship between classical atherosclerosis risk factors, such as LDL-cholesterol concentration and systolic blood pressure, and either Fas or FasL. Salvayre et al. documented that small oxidised LDL molecules (ox LDL) activated apoptosis that was mediated by receptors like Fas/FasL. These molecules initiate classical cascade of caspase-3 with all morphological and biochemical consequences of this process [17]. Thus, administration of drugs lowering LDL-CH concentration (in our study all patients received statins) inhibits apoptosis and stabilises the atherosclerotic plaque. Our findings showed also a correlation between blood pressure and lymphocyte CD95/95L expression. Konstadoulakis et al. revealed a similar relationship between other apoptotic markers (Bax) and hypertension. Similar relations with other atherosclerosis risk factors such as smoking, hyperlipidaemia and type 2 diabetes mellitus were not found [18]. However, the studies carried out by Japanese investigators revealed an association between FasL concentration and inflammatory risk factors for atherosclerosis (CRP) in patients with arterial hypertension [19].

Apoptosis of the cells found within atherosclerotic plaque may be one of the pathogenetical factors of atherosclerosis and may also play an important role in its instability (rupture of atherosclerotic plaque) and the development of ACSs. Thus, complete understanding of the programmed cell death process at the molecular level may contribute not only to better understanding of atherosclerosis pathogenesis within the plaque, but also may create new diagnostic, therapeutic and prognostic possibilities.

Conclusions

1. In patients presenting with ACS, increased expression of apoptotic proteins such as Fas and FasL on the surface of peripheral blood lymphocytes is observed.
2. Demonstrated correlations suggest a close relationship between atherosclerosis risk factors and expression of the examined apoptosis markers.

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Ocena wybranych markerów apoptozy Fas/FasL (CD95/CD95L) na limfocytach chorych z ostrym zespołem wieńcowym

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Streszczenie

Wstęp: Ostry zespół wieńcowy wywołany jest pęknięciem lub owrzodzeniem blaszki miażdżycowej, co inicjuje kaskadę procesów z degradacją macierzy międzykomórkowej włącznie i wydzieleniem cytokin powodujących śmierć komórek śródbłonka. Mechanizm ten odgrywa główną rolę w apoptozie. Apoptoza to jedna z postaci programowanej śmierci komórek, nazywana również śmiercią fizjologiczną. Jest mechanizmem regulacyjnym pozwalającym na usunięcie wytworzonych w nadmiarze i niepotrzebnych w danej chwili komórek. Proces apoptozy jest regulowany przez białka apoptotyczne, których ekspresja ujawnia się na limfocytach wyizolowanych z obszaru mięśnia sercowego. Główną rolę odgrywa aktywacja kompleksu Fas/FasL (przezbłonowe białka nadrodziny TNFR), inicjującego wewnątrzkomórkową kaskadę przemian. Cytoplazmatyczna cześć aktywowanego receptora Fas wiąże białko adaptacyjne FADD i powstały w ten sposób kompleks Fas-FADD aktywuje kaspazę-8, która inicjuje kilka proteaz cysteinowych kaspazy-3 uważanych za efektorowe w apoptozie. Ten cykl przemian odgrywa kluczową rolę w eliminacji obwodowych limfocytów T, komórek zapalnych i nowotworowych przy udziale komórek cytotoksycznych, CD8 oraz NK. Z kolei molekuły blokujące sygnały apoptozy to FAP-1, hamujące przekazywanie sygnałów z Fas na domeny regulatorowe, jak również FLIP, które zapobiegają tworzeniu się kompleksu FAS-FADD-FLICE tak zwanych białek adaptacyjnych, które są dalszym etapem przebiegu śmierci fizjologicznej komórek. W końcowej jej fazie dochodzi do cyklu przemian kaspaz, a regulatorami ograniczenia programowej śmierci komórki są białka inhibitorowe hamujące proces apoptozy, takie jak IAP oraz cząsteczka Bcl-2. Ta ostatnia należy do białek regulatorowych apoptozy. W jej składzie są zarówno molekuły antyapoptotyczne (Bcl-2, BAG), jak i cząsteczka proapoptyczna typu Bax. Przewaga ekspresji molekuł jednego typu nad drugim może w konsekwencji decydować o nadmiarze proliferacji nad rozpadem komórek i odwrotnie. Dane z literatury podkreślają udział zaburzeń w licznych schorzeniach. Proces ten odgrywa zasadniczą rolę w takich ostrych chorobach, jak posocznica, SIRS, ostra niewydolność wątroby, zawał mięśnia sercowego (MI), w chorobach przewlekłych, jak choroba Parkinsona, Huntingtona, reumatyczne zapalenie stawów, a także w zaburzeniach autoimmunologicznych, takich jak chociażby choroba Gravesa-Basedowa czy też zapalenie tarczycy typu Hashimoto.

Cel: Ocena ekspresji markerów apoptotycznych Fas/FasL (CD95/CD95L) na limfocytach krwi obwodowej.

Metodyka: Badano 3 grupy chorych – z ostrym MI (n=18, średni wiek 62±8 lat), niestabilną dławicą piersiową (n=31, średni wiek 62±10 lat) i grupę kontrolną (n=20, średni wiek 60±9 lat) – bez towarzyszących czynników ryzyka miażdżycy i bez parametrów stanu zapalnego. Badania cząsteczek proapoptotycznych Fas/FasL przeprowadzono przy użyciu cytometrii przepływowej. Ocenę parametrów zapalnych oraz tradycyjnych czynników ryzyka wykonano, wykorzystując metodę immunoenzymatyczną ELISA.

Wyniki: Przeprowadzone badania wykazały zwiększoną ekspresję cząsteczek Fas i FasL na powierzchni limfocytów krwi obwodowej u chorych z ostrym MI ($p < 0{,}001$; $p < 0{,}002$) i niestabilną dławicą piersiową ($p < 0{,}01$; $p < 0{,}02$) w porównaniu z grupą kontrolną. Wykazano dodatnią korelację pomiędzy stężeniem frakcji LDL cholesterolu i wartościami skurczowego ciśnienia tętniczego a odsetkiem CD95 ($p < 0{,}001$; $p < 0{,}01$) i CD95L ($p < 0{,}02$; $p < 0{,}03$) w grupie pacjentów z ostrym MI.

Wnioski: Wykazano, że zwiększona aktywacja białek apoptozy (Fas i FasL) na limfocytach krwi obwodowej, do której dochodzi przed początkiem ostrego niedokrwienia, może mieć istotny wpływ na niestabilność blaszki miażdżycowej i wystąpienie ostrego zespołu wieńcowego. Konsekwentna terapia przeciwmiażdżycowa hamująca proces apoptozy może prowadzić do stabilizacji blaszki miażdżycowej.

Słowa kluczowe: zawał mięśnia sercowego, niestabilna dławica piersiowa, apoptoza

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