Abstract. Human body reacts to physical, chemical and biological insults with a complex inflammatory reaction. Crucial components and executors of this response are endothelial cells, platelets, white blood cells, plasmatic coagulation system, and complement. Endothelial injury and inflammation are associated with elevated blood levels of cell membrane-derived microvesicles. Increased concentrations of microvesicles were found in several inflammatory reactions and diseases including acute coronary syndromes, stroke, vasculitis, venous thromboembolism, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, anti-phospholipid antibody syndrome, inflammatory bowel disease, thrombotic thrombocytopenic purpura, viral myocarditis, sepsis, disseminated intravascular coagulation, polytrauma, and burns. Microvesicles can modulate a variety of cellular processes, thereby having an impact on pathogenesis of diseases associated with inflammation. Microvesicles are important mediators and potential biomarkers of systemic inflammation. Measurement of inflammatory cell-derived microvesicles may be utilized in diagnostic algorithms and used for detection and determination of severity in diseases associated with inflammatory responses, as well as for prediction of their outcome. This review focuses on the mechanisms of release of microvesicles in diseases associated with systemic inflammation and their potential role in the regulation of cellular and humoral interactions.

Introduction

Inflammation is a system of defensive tissue reactions to pathogenic insults. Human body reacts to physical, chemical and biological insults with a complex of defensive reactions. Crucial components and executors of these reactions are endothelial cells, platelets, white blood cells, plasmatic coagulation system, and complement (Bone et al., 1992; de Jong et al., 2010; Singer et al., 2016). The inflammatory process at any level creates transient tissue or organ dysfunctions. An insult of extreme intensity, such as polytrauma, burns, poisoning, and sepsis, creates a systemic response. These reactions have a significant impact on morbidity and mortality through the initiation of multiple organ dysfunction and multiple organ failure (Bone et al., 1992; Balk, 2014). Biomarkers serve as indicators of biological processes, including pathologic processes or responses to therapeutic interventions. The goals of current research in this field are to find and evaluate biomarkers and important mediators and bystander molecules of systemic inflammation that would allow early detection, quantify severity of inflammatory processes, and predict the outcome (Bone et al., 1992; Cavaillon and Adrie, 2009; Singer et al., 2016). Potential biomarkers of inflammation include soluble mediators of protein, polysaccharide or lipid basic structure, cells participating in inflammatory reactions, and cell membrane-derived microvesicles (MV(s)) (Cavaillon and Adrie, 2009; Angus and Van der Poll, 2013; Burger et al., 2013; Larsen and Petersen, 2017). MVs may represent poten-
tional biomarkers of various cell functions and responses that can be detected and measured in the blood and other biological fluids. MVs may also play a significant role in cell-to-cell communication. MVs with distinct functions in inflammatory processes can be detected and measured, including identification of their origin based on the pattern of antigens of the cell from which they originate (Xu et al., 2016).

Detection and isolation of different types of MVs is essential to studying their function and interaction within the organism, tissues and cells, and to introducing them into the description of pathophysiologic processes in the human body including inflammation (Chironi et al., 2009; Burger et al., 2013; Vitkova et al., 2018b). Various techniques of MV isolation from body fluids are described in the literature including sequential centrifugation, density gradient centrifugation, filtration, and chromatography methods. Flow cytometry, enzyme-linked immunosorbent assay (ELISA), electron microscopy, dynamic light scattering (DLS), and nanoparticle tracking analysis (NTA) are widely used methods for MV analysis and measurement. Selection of the method for evaluating MVs depends on the ultimate goal of the analysis (Aupeix et al., 1997; Gelderman and Simak, 2008; Dragic et al. 2011; Yuana et al., 2011).

MVs are functionally active in the intercellular communication between extracellular vesicle-producing cells and the other cells, and they can be a potential biomarker for diagnosis, for the response to medical treatment by a therapeutic agent and for prognosis (Amabile et al., 2012; Fujita et al., 2014).

Inflammation, systemic inflammation and systemic inflammatory response syndrome (SIRS)

Inflammation is a system of defensive tissue reactions to the pathogenic insults. Its goal is to eliminate damaged tissues, foreign materials, and microorganisms and, subsequently, to enhance regeneration and repair of the tissues. Insults that cause an inflammatory response can be of diverse character: biological (microorganism, parasites), physical (trauma, radiation), chemical (toxins), metabolic (hypoxia, malnutrition, metabolic disorders), immunological (autoimmune diseases), and other endogenous disorders and exogenous triggers. The molecular stimuli triggering the inflammatory reaction fall into two general categories, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs represent structures conserved among microbial species such as bacterial lipopolysaccharides. DAMPs represent endogenous molecules released from damaged cells or cells in stress such as heat-shock proteins. PAMPs and DAMPs are recognized by specific transmembrane (e.g., Toll-like receptors, C-type lectin receptors) or cytoplasmic (e.g., RIG I-like receptors, NOD-like receptors) pattern recognition receptors (PRRs).

These PRRs are expressed in various cells. Sensing of PAMPs or DAMPs by PRRs results in activation of signalling pathways including nuclear factor-κB (NF-κB) and MAP kinases, leading to up-regulation of the transcription of genes involved in inflammatory responses (Takeuchi and Akira, 2010; Salvador et al., 2016). Interleukin-1 (IL-1) and tumour necrosis factor α (TNF-α) are among the cytokines released first. These inflammatory cytokines further amplify the pro-inflammatory cellular signalling through activation of the cleavage process of NF-κB inhibitor (IκB). NF-κB translocates to the nucleus, where it enhances expression of several other pro-inflammatory cytokines. The inflammatory response is mediated by cooperation of five complex cellular and humoral systems and their regulators: endothelial cells, platelets, white blood cells, plasmatic coagulation system, and complement. The response to an intensive insult triggers the inflammatory cascade, with production and release of various humoral regulators including cytokines.

Cytokines are released by monocytes, tissue macrophages, mast cells, platelets, and endothelial cells (Cavillon and Adrie, 2009). Pro-inflammatory cytokines either function directly on the tissue or via secondary mediators to activate the coagulation cascade and the complement cascade, with release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes (Sitia et al., 2010; Flanner et al., 2012). The results of this complex process may cause organ dysfunctions through specific and nonspecific damage to the tissues (Goris, 1996; Cavillon and Adrie, 2009). Inflammation is a reaction of a vascularized tissue to the insult (Fig. 1). The local reaction is limited to the injured tissue and causes transient tissue dysfunction with possible permanent functional and/or structural impairment. Systemic inflammation, caused by systemic progression of the local insult or systemic insult, is accompanied by multiple organ dysfunctions, which can lead to the progressive multiple organ dysfunction syndrome (MODS) or multiple organ failure as a result of intensive inflammation, and to death (Bone et al., 1992; Goris, 1996; Cavillon and Adrie, 2009).

The defensive inflammatory process of the human body represents a complex of pro-inflammatory and anti-inflammatory reactions. Regardless of the insult, the reaction of the body seems to be uniform, starting with a pro-inflammatory reaction; therefore, the name systemic inflammatory response syndrome (SIRS) is mostly used (Bone et al., 1992; Matsuda and Hattori, 2006; Robertson and CooperSmith, 2006; Tang et al., 2007; Lee et al., 2009; Lucignano et al., 2011; Balk, 2014; Davis et al., 2017; Sauaia et al., 2017). The aetiology of SIRS includes infectious diseases, surgical procedures, trauma, intoxications, and therapy complications. The clinical examples of the main infectious causes of SIRS are: bacterial sepsis, systemic candidiasis, systemic viral infections (influenza), toxic shock syndrome, and burn wound infections. The clinical examples of the main non-infectious causes of SIRS are:
autoimmune disorders, burns, poisoning, electrical tissue damage, haemorrhagic shock, malignancies, myocardial infarction, severe cardiac arrhythmias, pancreatitis, vasculitis, surgical procedures, and transfusion reactions (Pittet et al., 1995; Rangel-Fausto et al., 1995; Cavaillon and Adrie, 2009; Balk 2014; Singer et al., 2016). All cells participating in the inflammatory response produce MVs, and their distinction and quantification may help in finding new definitions and ways of detection and determination of the severity and progression of the infectious and non-infectious inflammatory process including SIRS (Burger et al., 2013).

**Cell-derived membrane MVs**

Eukaryotic cells release several types of membrane-derived extracellular vesicles (EVs). Cells release vesicles into extracellular space under both normal and stress conditions (Yamamoto et al., 2016). Detectable levels of EVs from different cell origins are commonly found in the plasma and other body fluids (Burnouf et al., 2015). They are produced by all somatic cells in the human body. Membranous vesicles are important mediators of physiological cellular processes, such as angiogenesis, stem/progenitor cell engraftment, and regul-
mechanisms of elimination of MVs. Phagocytosis appears to be the primary mechanism of MV elimination in vivo. The externalized phosphatidylserine may signal scavenger receptors to promote endocytosis of MVs (Jansen et al., 2012). Opossonized MVs might be endocytosed through the C3b or lactadherin receptors (Faille et al., 2012). Macrophages may discriminate and prioritize the clearance of MVs and other extracellular vesicles on the basis of glycosylation patterns (Burger et al., 2013). Certain types of MVs, such as thrombocyte MVs, might be phagocytosed by endothelial cells (Dasgupta et al., 2012; Faille et al., 2012). The rate of MV clearance from the circulation depends on the type of MVs analysed and temporal variations in experimental setups ranging from several minutes up to a few hours (Augustine et al., 2014).

Classification, function, and clinical relevance of MVs

Surface antigens of MVs reflect their cell origin and allow immunodetection of cell-specific MVs (Inzhutova et al., 2013). Individual types of EVs are released from cells by different mechanisms (Gould and Raposo, 2013). EVs are commonly classified into three major groups (Kalra et al., 2012) based on their theoretical biogenesis pathways and sizes (Table 1). MVs represent a heterogeneous subgroup of cell-membrane vesicular bodies, with sizes ranging from 100–1000 nm.

Formation and clearance of MVs during inflammation

Plasma concentrations of MVs are determined by a dynamic balance between the rate of their formation and elimination. Acute and chronic inflammatory processes are characterized by increased concentration of MVs in the blood. Various bacterial toxins, inflammatory cytokines, reactive oxygen species, and coagulation factors initiate formation of MVs from cells participating in the inflammatory reaction (Yong et al., 2013; Cognassee et al., 2015). The cell sources of inflammation-associated MVs and stimuli leading to their release are summarized in Table 2. Less information is available about the mechanisms of elimination of MVs. Phagocytosis appears to be the primary mechanism of MV elimination in vivo. The externalized phosphatidylserine may signal scavenger receptors to promote endocytosis of MVs (Jansen et al., 2012). Opossonized MVs might be endocytosed through the C3b or lactadherin receptors (Faille et al., 2012). Macrophages may discriminate and prioritize the clearance of MVs and other extracellular vesicles on the basis of glycosylation patterns (Burger et al., 2013). Certain types of MVs, such as thrombocyte MVs, might be phagocytosed by endothelial cells (Dasgupta et al., 2012; Faille et al., 2012). The rate of MV clearance from the circulation depends on the type of MVs analysed and temporal variations in experimental setups ranging from several minutes up to a few hours (Augustine et al., 2014).

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et al., 2012; Reid and Webster, 2012; Burger et al., 2013; Wu et al., 2013; Trzepizur et al., 2014; Deng et al, 2017) (Table 3).

### MVs in local and systemic inflammation

MVs play a crucial role in inflammation. The release of platelet, endothelial and leukocyte MVs is in general increased during inflammation. MVs from certain cells may induce and modulate the inflammatory response. MVs up-regulate synthesis of numerous inflammatory cytokines, enzymes and other soluble mediators of inflammation. MVs can also promote expression of cell adhesion molecules in endothelial cells. Aminophospholipids of MVs may represent substrates for production of lysophosphatidic acid, arachidonic acid and other lipid mediators of inflammation (Wu et al., 2013). On the other hand, inflammatory cytokines, such as TNF-α and IL-1, potentiate MV generation by target cells (Cloutier et al., 2013).

#### Platelet MVs

Activation of platelets represents an inherent part of the inflammatory reaction. Platelet MVs accumulate at the sites of vascular injury on leukocytes and on activated endothelium. These MVs can contribute to leukocyte-leukocyte interactions through the binding of P-selectin and P-selectin glycoprotein ligand 1 (PSGL-1) (Nomura et al., 2000). Platelet MVs may increase recruitment of immune cells such as monocytes, T and B lymphocytes, and natural killer cells and modulate the inflammatory processes. A high concentration of costim-
ulmonary ligand CD40L/CD154 on platelet MVs may contribute to antigen-specific adverse reactions to platelet transfusion and transfusion-related acute lung injury (Blumberg et al., 2006; Khan et al., 2006). Platelet MVs support transcellular transport of arachidonic acid to increase expression of cyclooxygenase 2 (COX-2) in a human monocyte cell line, which converts arachidonic acid to prostaglandin endoperoxide H2, an important precursor of prostacyclin (Barry et al., 1999).

Prostacyclin is an important effector molecule that induces vasodilatation and inhibits proliferation, angiogenesis, platelet adhesion, and aggregation and has an anti-inflammatory effect through a stimulatory effect on the expression of anti-inflammatory cytokines (e.g., IL-10) and inhibitory effect on the expression of pro-inflammatory cytokines (e.g., IL-1 and IL-6) (Nomura and Shimizu, 2015). The complexity of the effect of platelet MVs on target cells underlines that they can stimulate production of pro-inflammatory cytokines IL-1, IL-6, IL-8, TNF-α, monocyte chemoattractant protein 1 (MCP-1), and other pro-inflammatory molecules through a direct ligand-receptor interaction (Wu et al., 2013; Cognasse et al., 2015). These cytokines activate inflammatory cells to generate more MVs, forming a positive feedback loop.

Endothelial MVs

Endothelial cells activated by endotoxin or inflammatory cytokines produce tissue factor-rich MVs with pro-coagulation properties. The ability of endothelial MVs to bind coagulation factors and promote thrombin generation has been described in vitro and also in several inflammatory conditions such as acute coronary syndrome and hypoxia-reoxygenation injury (Deng et al., 2017). Tissue factor-rich endothelial MVs bound to monocytes and platelets amplify the inflammatory process and disseminate the pro-coagulant potential. MVs released by activated endothelial cells can bind to unperturbed endothelial cells and induce increased expression of cell adhesion molecules and facilitate monocyte-endothelial cell interactions. Endothelial MVs have also been shown to bind to monocytes and promote their trans-endothelial migration (Cognasse et al., 2015). Tissue factor-rich endothelial MVs released by microvascular endothelial cells can overcome the consequences of arterial occlusion and tissue ischaemia by promoting post-ischemic neovascularization and tissue reperfusion (Arderiu et al., 2015).

White blood cell MVs

In vitro experiments have shown that MVs derived from activated polymorphonuclear leukocytes promote release of inflammatory cytokines IL-1, IL-6, IL-8, monocyte chemoattractant protein (MCP-1), TNF-α, and other molecules involved in the regulation of inflammation (Wu et al., 2013; Cognasse et al., 2015). Monocyte MVs have been reported to increase expression of cell adhesion molecules on the target cells through activation of NF-κB translocation to the nucleus. MVs released by leukocytes can stimulate expression of proangiogenic chemokines CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, and CXCL8 by synovial fibroblasts. T-cell-derived MVs have been reported to promote production of TNF-α and IL-1β by monocytes (Distler et al., 2005).

Red blood cell MVs

Increased levels of erythrocyte MVs are associated with haemolytic diseases, such as thalassemia, paroxysmal nocturnal haemoglobinuria, and sickle cell anemia. They are suggested to be involved in activation of coagulation, fibrinolysis, and endothelial activation (Simmak et al., 2004; van Beers et al., 2009).

MV and diseases with acute inflammatory processes

Increased plasma MV levels were reported in several acute inflammatory diseases (Table 4). MVs stimulate production and release of inflammatory cytokines, and these induce formation of MVs by a positive feedback loop. The MV plasma concentration may distinguish acute and chronic inflammatory processes in the organism and can be useful for determination of the severity of disease. Increases in MVs of various origins were reported in acute coronary syndromes. Elevations in plasma levels of platelet and endothelial MVs predict cardiovascular morbidity and mortality (Sinning et al., 2011; Amabile et al., 2012). Increases in neutrophil-derived MVs have been reported in anti-neutrophil cytoplasmic autoantibody-associated vasculitis (Hong et al., 2012). Increases in endothelial, erythrocyte, platelet and leukocyte MVs were reported in the graft-versus-host disease (Lia et al., 2018). MVs are increased in hypercoagulation states. Elevations in MVs of various origins have been proposed as a predictor of deep vein thrombosis (Park et al., 2012; Thaler et al., 2012). The concentration of MVs in circulating blood depends on the rate of their formation and clearance. However, there is still insufficient scientific evidence of the rate of MV formation and clearance both in the health and in disease states.

MV in sepsis and systemic inflammation

Sepsis is a clinical syndrome characterized by a systemic inflammatory response to infection. The systemic inflammatory response is characterized by activation of the coagulation system, inhibition of anticoagulant mechanisms, and fibrinolysis, which can lead to disseminated intravascular coagulation with microvascular thrombosis. Up-regulation of the inflammatory responses and neuroendocrine system activity leads to vascular hyporeactivity and enhanced apoptosis of the involved tissue cells, which may contribute to multiple organ dysfunction and septic shock (Annan et al., 2005). Endothelial dysfunction with increased endothelial permeability, increased levels of nitric oxide, reduced vascular reactivity to nitric oxide, and reactive oxygen species
(ROS)-induced oxidative stress are important pathogenic mechanisms in the sepsis (Kirkeboen and Strand, 1999). Established experimental models of sepsis showed direct induction of MV release that may cause the endothelial activation (Brown and McIntyre, 2011). Experimental data suggest that MVs have a pro-inflammatory effect in the sepsis. Raised levels of platelet, granulocyte, and endothelial MVs were reported in patients with meningococcal sepsis (Reid and Webster, 2012). MVs have pro-coagulant activity with thrombin generation via a tissue factor-dependent mechanism. Enhanced coagulation mediated by MVs was described in disseminated intravascular coagulation (Aras et al., 2004).

Production of leukocyte MVs is increased in association with increased oxidative activity. Circulating levels of monocyte MVs were reduced in sepsis and may reflect monocyte dysfunction in severe sepsis. Leukocytes activated during the sepsis produce MVs with increased exposure of adhesion molecules on the surface. Interaction between activated leukocyte MVs and endothelial MVs through adhesion molecules is enhanced in patients with SIRS (Nieuwland et al., 2000). Septic patients’ MVs induce ROS production and apoptosis of endothelial cells and smooth muscle cells in vitro through a NADP oxidase-dependent pathway (Reid and Webster, 2012). Rats inoculated with MVs isolated from septic rats exhibited an increase in superoxide anion.
production, NF-κB activation, enhanced expression of nitric oxide synthase 2 (NOS-2), and overproduction of nitric oxide in the vascular wall (Mortaza et al., 2009). MVs from septic shock patients enhanced sensitivity of contraction of the mouse aorta to serotonin, suggesting a protective effect against vascular hyporeactivity during sepsis (Mostefai et al., 2008). Such protective effects may be important during the early phase of septic shock by compensating for vascular hyporeactivity associated with hypotension (Lafer, 2011).

Systemic inflammation and sepsis are often accompanied by the acute respiratory distress syndrome (ARDS). ARDS is associated with the presence of MVs in the alveolar space. Higher levels of leukocyte MVs in the blood and bronchoalveolar lavage of ARDS patients were associated with a better outcome in early-stage disease. This suggests that MVs may play a protective role in the pathogenesis of ARDS and may serve as a biomarker of prognostic significance (Guervilly et al., 2011). Raised levels of circulating platelet, granulocyte, and endothelial MVs were identified in patients with meningococcal sepsis and septic shock, severe trauma, and traumatic brain injury (Nieuwland et al., 2000; Fujimi et al., 2002). High levels of endothelial MVs were associated with vascular dysfunction and may contribute to tissue hypoperfusion and organ dysfunction (Forest et al., 2010). Septic shock patients’ MVs exert pleiotropic and variable effects on target tissues. MVs obtained from patients with early-stage septic shock injected into mouse circulation induced expression of proinflammatory proteins NOS-2, COX-2, and NF-κB in the heart and lungs, along with increased oxidative and nitrination stress. Increased oxidative stress was also detected in the liver and to a lesser extent in the kidneys (Mastronardi et al., 2011). This suggests that blood-derived septic shock MVs may contribute to pathogenesis of organ dysfunction in the septic shock. Elevated levels of platelet, endothelium, and leukocyte MVs predict unfavorable outcome in severe sepsis (Reid and Webster, 2012). Endothelial MVs carry functional endothelial protein C receptor (CD201) and contribute to enhanced thrombogenicity via consumption of activated protein C (Morel et al., 2009).

Limited information is available on the role of MVs in non-septic SIRS. Elevated levels of leukocyte MVs were found in patients with burn injury (O’Dea et al., 2016). Hypoxic ischemic insult leading to systemic inflammatory response with multiple organ dysfunction was associated with increased levels of MVs in newborns (Vitkova et al., 2018a). Recent publications that focus on the role of MVs in septic and non-septic systemic inflammatory response are shown in Table 5. MVs produced during the systemic inflammatory response may participate in vascular and endothelial dysfunction, leading to circulatory failure, tissue injury and organ dysfunction (Reid and Webster, 2012). On the other hand, several clinical and experimental studies suggest a protective role of MVs during the sepsis. The mechanisms of contribution of MVs derived from individual cell types in systemic inflammation and their role in pathogenesis are thus still unclear. However, the levels of MVs in the blood may serve as important indicators of systemic inflammation.

### Conclusion

Inflammation is associated with elevated blood levels of MVs. MVs released by activated endothelial cells, red blood cells, platelets, and white blood cells modulate a variety of cellular processes, thereby having an impact on the pathogenesis of diseases associated with inflammation. To better understand how MVs achieve their biological effects, studies focusing on determination of their origin and their clearance in the health and disease are essential. Future research relating to MVs should focus on the optimization and implementation of

### Table 5. Blood MV analysis in systemic inflammatory response

<table>
<thead>
<tr>
<th>Inflammatory disease</th>
<th>Type of MVs</th>
<th>Result</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Elevated levels of leukocyte, granulocyte, platelet and endothelial MVs</td>
<td>Pro-inflammatory and pro-coagulant activity</td>
<td>Nieuwland et al., 2000</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
<td>Elevation of endothelial MVs</td>
<td>Level of endothelial MVs is increased in DIC induced by septic shock</td>
<td>Delebranche et al., 2013</td>
</tr>
<tr>
<td>Polytrauma</td>
<td>Elevated levels of MVs and platelet MVs</td>
<td>Level of platelet MVs negatively correlated with mortality</td>
<td>Curry et al., 2014</td>
</tr>
<tr>
<td>Burns</td>
<td>Elevated levels of leukocyte MVs</td>
<td>Markedly increased granulocyte and monocyte MVs in patients following burn injury and their potential role in progression to sterile SIRS</td>
<td>O’Dea et al., 2016</td>
</tr>
<tr>
<td>Hypoxia and multiple organ dysfunction syndrome</td>
<td>Increased level of MVs</td>
<td>Increased level of MVs and mucosal endothelial MVs in newborns on extracorporeal membrane oxygenation</td>
<td>Vitkova et al., 2018a</td>
</tr>
</tbody>
</table>
standardized pre-analytical and analytical processing of samples. An important step in our understanding of the biological effects of MVs is development of selective agents with the ability to modulate MV release, function and clearance.

Disclosure of conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

The authors would like to acknowledge Klára Ulecová for the graphical work. J. J. and J. Z. contributed equally.

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