MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Inflammatory Mechanisms and Treatment of Myocardial Infarction

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Abstract

Myocardial infarction (MI) is the most severe manifestation of coronary artery disease which may lead to heart failure. One of the crucial mechanisms causing MI induced complications is inflammasome activation and subsequent release of inflammatory cytokines. A significant rise in troponin I, creatine kinase-MB (CK-MB), interleukin 1β (IL-1β) serum levels and nuclear factor-kappa B (NF-κB) were observed in MI. Moreover, increase in the expression of all inflammasome components was detected along with histopathological and electrocardiographic abnormalities. The current mini-review shows that targeting the inflammatory cascade through inflammasome inhibition may be a novel strategy for management of MI and preventing its complications.

Keywords: Inflammasome, NF-κB, Myocardial infarction.

1. Introduction

Myocardial infarction is one of the most prevalent cardiovascular diseases **(Gabriel-Costa et al., 2018)**. Over the past years, treatment increased survival among patients having acute MI. However, the risk of heart failure post MI remains high and it increased parallel to the decrease in mortality **(Frangogiannis, 2012)**. After an infarction, the heart undergoes a series of structural changes ruled by cellular and molecular mechanisms known as ventricular remodeling. This process is followed by a decline in left ventricular performance, demonstrated as diminished systolic function and reduced stroke volume **(Gajarsa & Kloner, 2011)**. Consequently, therapies are required to reduce MI size and avoid ventricular remodeling to reduce the onset of heart failure **(Hausenloy et al., 2017)**.

2. Inflammation and MI

Due to limited regenerative ability of the heart, the healing of infarcted cells depends on formation of collagen-based scar through three phases: inflammatory phase in which intense transient inflammatory reaction is activated to clear the infarcted area of extracellular matrix debris and infarcted cells. Then, proliferative phase begins and reparative cells such as myofibroblasts produce extra cellular matrix proteins to maintain left ventricle integrity. Finally, maturation phase in which scar is formed **(Frangogiannis, 2012)**. The inflammatory cascade is one of the purposed mechanisms of deteriorating MI as it contributes to adverse left ventricular remodeling which can lead to heart failure **(Westman et al., 2016; Gabriel-Costa et al., 2018)**. The NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome plays a crucial role in the inflammatory cascade of MI. As a result, it may act as a good target to improve the outcomes of MI **(Timmers et al., 2008)**.

3. Inflammasome Activation

Activation of NLRP3 inflammasome needs two

steps. Firstly, NF-κB must be stimulated due to activation of TLR4 by injured cardiac cells **(Timmers et al., 2008)**. This leads to increased expression of NLRP3 protein and pro-interleukin 1β (IL-1β) **(Timmers et al., 2008; Bauernfeind et al., 2009)**. Secondly, moving of the NLRP3 to the mitochondria, releasing of mitochondrial contents into the cytosol as reactive oxygen species (ROS), potassium efflux and increasing of intracellular calcium **(Lee et al., 2012; Murakami et al., 2012)**. When ROS are released, TXNIP binds to NLRP3 to promote inflammasome stimulation **(Harper et al., 2019)**. This is followed by activation of caspase-1 which changes pro- IL-1β to its active form causing stimulation of multiple inflammatory processes **(Guo et al., 2015) (Figure 1)**.

4. Treatment

4.1. Non-ST-Elevation Myocardial Infarction (NSTEMI)

4.1.1. Standard medical therapy

Oxygen is supplied for patients with hypoxemia. Nitrates are administered sublingually for ischemic pain and if pain is persistent or patient is hypertensive or has heart failure they are intravenously administered **(Peacock et al., 2004)**. Morphine may be administered intravenously as an analgesic to relieve continuing chest pain despite being treated with anti-ischemic drugs **(Conticon, 2011)**. Oral beta blockers should be started in the first 24 hours unless contraindicated **(Kontos et al., 2011)**. High intensity statins should be administered **(Cannon et al., 2006)**.

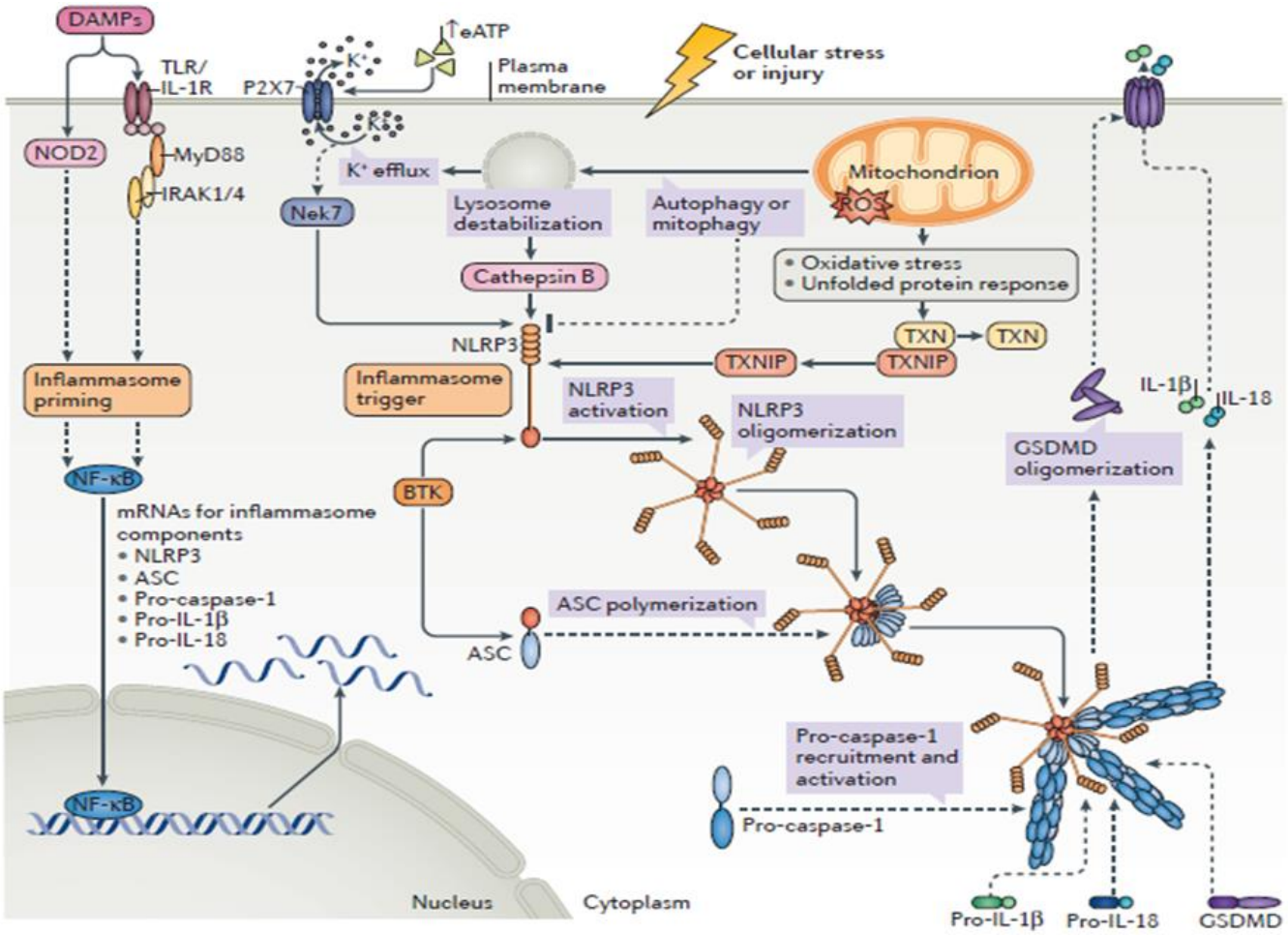

Figure 1: Inflammasome activation **(Toldo & Abbate, 2018)**.

4.1.2. Antiplatelet – Anticoagulation therapy

Aspirin is administered to all patients after presentation and then maintenance dose is given indefinitely **(Mehta et al., 2010)**. P2Y12 inhibitors as clopidogrel are administered with aspirin for 12 months **(Mahaffey et al., 2011)**. Glycoprotein 2b/3a inhibitors can be used in patients treated with early invasive strategy, dual anti platelet therapy and with intermediate or high-risk features **(Boersma et al., 2000; Giugliano et al. 2009)**. Anticoagulation therapy is recommended for all patients **(Antman et al., 1999)**.

4.1.3. Inhibitors of the Renin-Angiotensin-Aldosterone System

Angiotensin converting enzyme inhibitors (ACEIs) are given for patients having left ventricular ejection fraction (LVEF) below 40%, stable chronic kidney disease, diabetes or hypertension **(Garg & Yusuf, 1995)**. Angiotensin receptor blockers are recommended in patients who cannot tolerate ACEIs and having LVEF <40% or having heart failure **(Yusuf et al., 2008)**. Aldosterone blockers are used in patients taking ACEIs and beta blockers and having LVEF< 40% or diabetic or having heart failure unless contraindicated, also they can be used in patients who are ACEIs intolerant **(Pitt et al., 2003)**.

4.1.4. Invasive treatment

Invasive treatment strategy is needed in patients having refractory angina or having hemodynamic instability or electrical instability if there are no contraindications **(Cannon et al., 2001; Damman et al., 2010)**. Invasive treatment strategy can be used in stabilized patients with high risk for clinical events **(Cannon et al., 2001)**.

4.2. ST-Elevation Myocardial Infarction (STEMI)

4.2.1. Reperfusion therapy selection

Reperfusion therapy is indicated if ischemia symptoms appeared within 12 hours with persistence of ST elevation **(Boersma & Primary Coronary Angioplasty vs. Thrombolysis Group, 2006)**. Primary percutaneous intervention (PCI) is preferred over fibrinolysis if within right time frame **(Andersen et al., 2003)**. If Primary PCI cannot be performed in right time, frame fibrinolysis is recommended within 12 hours of symptoms appearance if not contraindicated. If patient symptoms onset is over 12 hours and still suffering from symptoms suggestive of ischemia or life-threatening ischemia or hemodynamic instability, then primary PCI is needed **(Gierlotka et al., 2011)**. Routine primary PCI can be used in late presenting patients (12-48 hours) after symptom onset **(Schömig et al., 2005; Busk et al., 2009; Ndrepepa et al., 2009)**.

4.2.2. Antiplatelet – Anticoagulation therapy with primary percutaneous coronary intervention (PCI)

Aspirin is indicated for all STEMI patients unless contraindicated **(Patrono et al., 2011)**. P2Y12 inhibitors are indicated before PCI and 1 year after PCI unless contraindicated **(Wallentin et al., 2009)**. Glycoprotein 2b/3a inhibitors can be used if there are signs of thrombotic complication or no reflow. Anticoagulation therapy is needed for all patients undergoing primary PCI **(Ibanez et al., 2018)**.

4.2.3. Fibrinolysis therapy

If fibrinolysis is the chosen strategy, it should be initiated as soon as possible after the diagnosis **(Bonnefoy et al., 2009)**.

4.2.4. Antiplatelet – Anticoagulation therapy with fibrinolysis

Aspirin and clopidogrel are indicated in patients undergoing fibrinolysis **(Sabatine et al., 2005)**. Dual antiplatelet therapy (DAPT) is continued for 1 year after fibrinolysis **(Ibanez et al., 2018)**. Anticoagulation is recommended until revascularization or for hospital stay duration up to 8 days (**Peters et al., 2008)**.

4.2.5. Interventions following fibrinolysis therapy

Transferring to a PCI capable facility after fibrinolysis is recommended immediately. Rescue PCI is needed immediately when fibrinolysis therapy failed or in case of worsening or recurrent ischemia or hemodynamic instability or electrical instability or evidence of re-occlusion after successful treatment with fibrinolysis **(Armstrong et al., 2013)**.

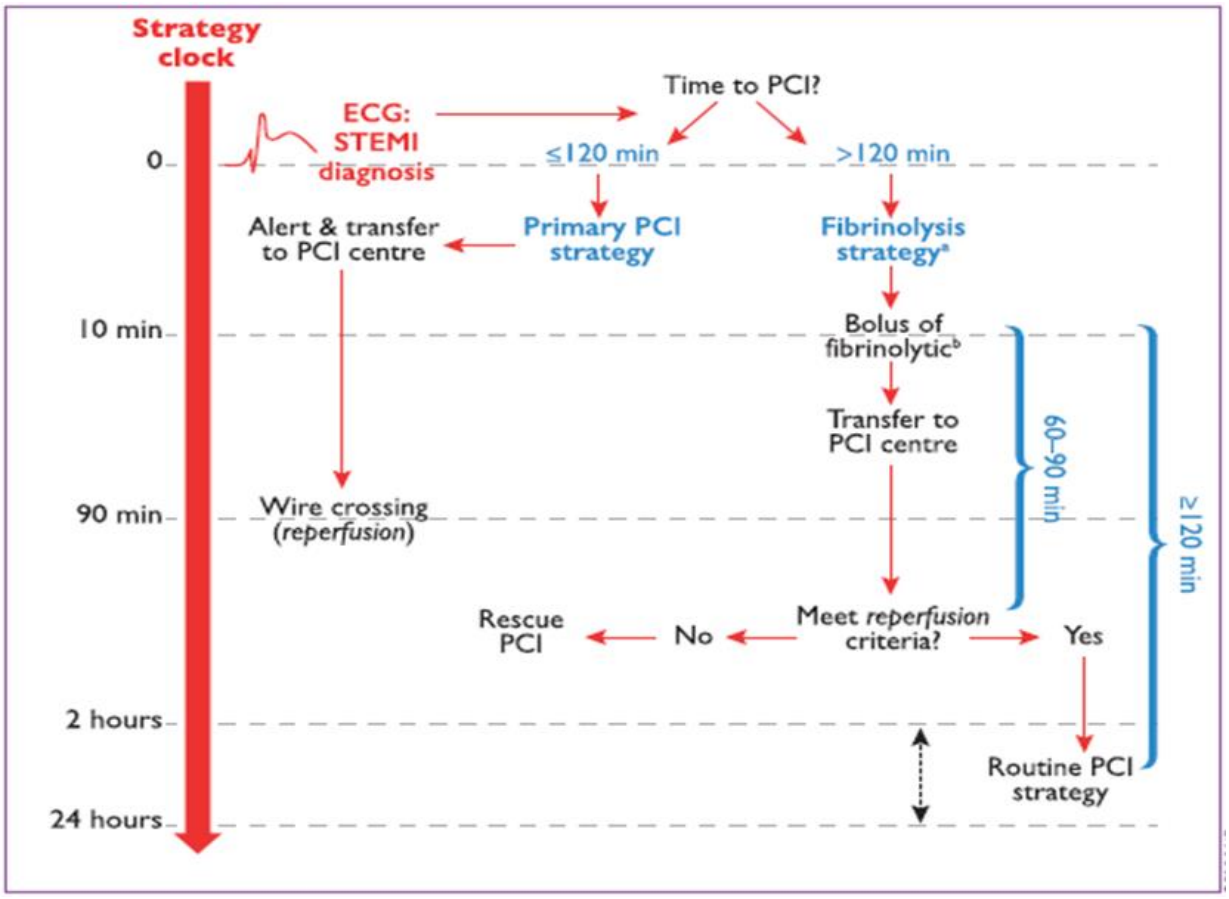

Figure 2: STEMI management timing **(Ibanez et al., 2018)**.

4.2.6. Coronary artery bypass graft surgery (CABG)

It should be considered if PCI cannot be performed due to unsuitable anatomy for PCI or if patient has cardiogenic shock or large part of myocardium is at risk **(Hochman et al., 1999)**.

5. Conclusion

Despite the progress made in MI treatment, MI still causes many complications such as heart failure. Inflammation is one of the main mechanisms causing MI complications, so it is one of the main promising targets to be targeted by novel therapies to decrease MI complications.

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