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New Therapeutic Application of Erythropoietin Against Ischemic Heart Diseases

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Erythropoietin (EPO) is a cytokine that promotes proliferation and differentiation of erythroid precursor cells, and it is widely used for the treatment of anemia in patients with chronic renal failure (1). Therefore, EPO has been classified as one of the hemopoietic cytokines independent of cardiovascular physiological and biochemical actions. However, intriguingly, EPO can also exert anti-apoptotic and radical scavenging effects on non-erythroid cells (1). Furthermore, EPO receptors are found in cardiovascular systems including endothelial cells and cardiomyocytes (2). These findings suggest that EPO is expected to have some function in cardiovascular systems. Indeed, several investigators showed that an administration of EPO before or shortly after the onset of ischemia reduced myocardial infarct size and improved cardiac function in acute phases (3, 4). Another interesting non-erythroid function of EPO is the promotion of endothelial progenitor cell (EPC) mobilization in animals and humans, which may enhance neovascularization of ischemic areas (5, 6). Recently, Hirata et al. demonstrated that EPO increased EPC and enhances angiogenesis in ischemic myocardium after myocardial infarction (MI) and simultaneously improved cardiac function (7).

Along with these lines of evidence, Nishiya et al. importantly investigated effects of EPO on cardiac remodeling after MI in rats (8). They administered EPO in two different ways: Subcutaneous injection once a day for 4 days at 5,000 U/kg or 3 times a week for 4 weeks at 1,000 U/kg. They found that EPO improved both hemodynamic parameters and cardiac function after MI in both experimental groups. They also found

that EPO prevented caspase-3 activation, up-regulation of remodeling-related genes, and the increase in interstitial fibrosis in non-infarcted myocardium. Finally, they showed enhanced angiogenesis and reduced apoptosis in the peri-infarcted myocardium. Their findings provide additional important evidence that EPO exerts cardioprotective effects after ischemia/reperfusion injury. However, if EPO is to be used in clinical applications, there are several important considerations.

Therapeutic dose and time-window

Nishiya et al. demonstrated that the administration of EPO (1,000 – 5,000 U/kg) improved cardiac function after a complete occlusion model of MI (8). The doses of EPO administered were nearly 10 times higher than those clinically used in anemic patients with chronic renal failure (1). Hirata et al. demonstrated that EPO dose-dependently (100 – 1000 IU/kg) reduced infarct size in a canine model of ischemia/reperfusion (7). Further investigation will be needed to determine the optimal dose of EPO for exerting cardioprotective effects in clinical use.

The timing for EPO administration is another important issue that must be solved to apply this agent in clinical practice. Nishiya et al. administered EPO in two different ways: Subcutaneous injection once a day for 4 days or 3 times a week for 4 weeks (8). Several investigators showed that an administration of EPO before or shortly after the onset of ischemia reduced myocardial infarct size and improved cardiac function in acute phases (3, 4). Interestingly, van der Meer et al. demonstrated that EPO started three weeks after MI increased capillary density and simultaneously improved cardiac function in rats with MI (9). Further investigations will be also needed to determine the optimal timing

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and dose when EPO is applied in clinical practice.

Potential mechanisms by which EPO induces cardioprotection

Reduction of apoptotic cell death

Consistent with previous studies (3, 4), Nishiya et al. demonstrated that EPO decreased the number of TUNEL-positive cells in the peri-infarcted myocardium, suggesting that EPO prevents apoptotic cell death (8). However, since the TUNEL method also detects single strand breaks occurring in the course of necrotic cell death, it is likely that EPO attenuates apoptotic and necrotic cell death. Indeed, if EPO only inhibits the apoptotic cell death, it may be difficult to explain the marked reduction of infarct size by EPO. Recent reports suggest that EPO can inhibit the release of free radicals from neutrophils and act as a radical scavenger (1), both of which may reduce cardiac cell death after ischemia/reperfusion and attenuate cardiac remodeling.

Angiogenesis

Nishiya et al. showed enhanced angiogenesis in the peri-infarcted myocardium, which may contribute to the improvement of cardiac function after MI (8). Consistent with their report, we also found that EPO increased the number of EPC and angiogenesis in the ischemic myocardium (7). Interestingly, Nishiya et al. demonstrated that long-term administration of EPO significantly increased vessel density compared to short-term administration of EPO. Although EPO is a powerful stimulator of EPC mobilization from the bone marrow, it also has pro-angiogenetic effects (10). These different angiogenetic effects of EPO might explain the result of Nishiya's study.

Prevention of remodeling in the non-infarcted areas

Recent studies have highlighted the importance of fibrosis of non-infarcted areas remote from the site of infarction for the pathogenesis of post-infarction cardiac dysfunction (11, 12). Nishiya et al. clearly demonstrated that EPO prevented caspase-3 activation, up-regulation of remodeling-related genes, and the increase in interstitial fibrosis in non-infarcted myocardium. Prevention of cardiac remodeling in the non-infarcted myocardium will also contribute to the EPO-induced improvement of cardiac function after MI.

Clinical relevance

Recently, a higher endogenous EPO level can predict a smaller infarct size in patients with acute MI subjected to successful primary percutaneous coronary interven-

tion (13). These findings support the idea that an administration of EPO would exert cardioprotective effects against acute ischemia reperfusion injury and cardiac remodeling. However, we must be careful of thromboembolism when we apply EPO in the clinical situation. A high dose (40,000–60,000 IU per week) of subcutaneously administered EPO increased the incidence of thrombotic events such a venous thrombosis or pulmonary embolisms in patients with breast cancer (14). On the other hand, in a previous clinical study, a high dose (33,000 IU once daily for the first 3 days) of intravenously administered EPO was well tolerated in patients with stroke and improved clinical outcome at 1 month (15). Careful clinical study will be warranted if EPO is to be applied for the treatment of patients with acute MI.

Although considerable future work will be required, EPO is a potentially promising candidate for an adjunctive therapy for acute MI and cardiac remodeling, and Nishiya et al. largely and importantly contributed to the paradigm of EPO in the field of cardiovascular protection.

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