Cardiac repair: Neutrophils to the rescue

February 10 2016

Following an acute heart attack, immune cells called neutrophils coordinate an inflammatory response which can exacerbate the damage to the organ. Now researchers from Ludwig-Maximilians-Universitaet (LMU) in Munich have shown that neutrophils also promote cardiac repair.

According to a new study led by Sabine Steffens, Professor of Clinical Pathobiochemistry in the Institute for Cardiovascular Prevention (IPEK) at the LMU Medical Center, neutrophilic granulocytes, commonly referred to as neutrophils, play a crucial role in the repair of the damaged cardiac tissue in the aftermath of a heart attack. "This is a surprising result, because neutrophils have been thought to have a purely deleterious effect on the heart tissue following acute myocardial infarction, she says. The findings appear in the *European Heart Journal*.

Heart attacks are associated with a localized breakdown in the supply of oxygen to the organ, which results in the death of large numbers of cardiac muscle cells. The ensuing distress signals released by dying cells alert the immune system, and neutrophils rapidly migrate to the site of damage. These cells are specialized for the uptake of particulate matter, such as cell debris and invading pathogens, but they also induce an acute inflammatory reaction by secreting chemical messengers that mobilize other types of immune cells. The latter is an essential step, as it serves to initiate the process of tissue repair by accelerating the disposal of cells damaged by the infarct. However, the inflammation process eventually leads to the formation of scars, which effectively reduce the contractility of the muscle tissue. This in turn often triggers progressive heart failure,

which requires long-term medical surveillance and treatment.

Balancing conflicting demands

Sabine Steffens and her research group have now found that, in addition to initiating the inflammatory reaction, neutrophils actively promote repair of the damage caused by the heart attack. They do so by producing a factor that mediates the differentiation of a distinct class of macrophages, which stimulate the local repair process. "Inflammation reactions need not be exclusively deleterious. On the contrary, they are an essential part of the normal wound-healing mechanism, and the positive role of the neutrophils in this latter process has been overlooked," Steffens explains. As the new study reveals, neutrophils are in fact crucially involved in the resolution of post-infarct inflammation and the remodeling of damaged cardiac tissue.

The new findings confirm that the function of neutrophils is not yet fully understood. Moreover, the study has implications for novel therapeutic approaches under investigation to the treatment of infarct patients, which involve reducing the numbers of neutrophils at the site of injury in order to limit the extent of the inflammation. "It's a matter of finding the right balance between the opposing effects. There may well be a threshold value at which the positive impact of the neutrophils is adversely affected," Steffens points out. In other words, anti-inflammatory therapies may end up by actually impeding the repair process. It might therefore be a better idea to try and boost the development of the class of macrophages that promotes repair. Steffens and her team therefore plan to identify and dissect the signal pathways and regulatory mechanisms that stimulate the differentiation of these cells.

More information: Michael Horckmans et al. Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a

reparative phenotype, *European Heart Journal* (2016). DOI: 10.1093/eurheartj/ehw002