Immunity strikes: heart failure as a systemic disease

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This editorial refers to ‘Monocyte subset accumulation in the human heart following acute myocardial infarction and the role of the spleen as monocyte reservoir†, by A.M. van der Laan et al. on page 376

Chronic heart failure (CHF) is a rapidly growing health-care problem affecting 1 in 10 people over 70 years old. The prognosis and quality of life for CHF patients are as grim as in many malignancies. The most common reason for CHF is a myocardial infarction that was not reperfused in time, leading to myocardial remodelling. For remodelling, the sequential activation and deactivation of the immune system after cardiac ischaemia has an important role for adaptive and maladaptive processes. In the present issue, van der Laan et al. add an important puzzle piece to this picture by demonstrating monocyte infiltration in distinct regions within human infarcted myocardium.

Monocytes and myocardial infarction

The central role for monocytes after myocardial infarction was only recently demonstrated, especially by Matthias Nahrendorf’s group based on the mouse myocardial infarction model. Inflammatory Ly-6C<sup>high</sup> monocytes are among the earliest leukocytes to infiltrate the heart during the early pro-inflammatory phase. This is followed by recruitment of Ly-6C<sup>low</sup> monocytes, which promote granulation tissue formation, and finally the formation of a stable scar. Mouse data clearly indicate that this biphasic sequence of monocyte recruitment is a prerequisite for proper healing, as demonstrated by the observation that a sustained Ly-6C<sup>high</sup> monocyteosis worsens myocardial repair in apoE<sup>−/−</sup> mice. The absence of monocytes in general leads to deleterious healing and left ventricular cavity thrombus formation early after infarction. These animal data indicate that an adequate activation of monocytes/macrophages is a prerequisite for proper healing after myocardial ischaemia.

By analogy to murine data, human monocytes subsets defined by the surface expression pattern of CD14 and CD16 were also shown by an independent group to correlate with the clinical outcome after myocardial infarction. In humans, ‘inflammatory’ CD14<sup>+</sup>CD16<sup>+</sup> cells correspond to Ly-6C<sup>+</sup> monocytes/macrophages in mice, and CD14<sup>+</sup>CD16<sup>−</sup> cells to ‘anti-inflammatory’ Ly-6C<sup>−</sup> monocytes/macrophages in mice. Tsuijoka et al. found that peak levels of the ‘inflammatory’ CD14<sup>+</sup>CD16<sup>+</sup> subset correlated negatively with recovery of left ventricular function. Enhancement of CD14<sup>+</sup>CD16<sup>−</sup> monocytes after reperfusion was associated with microvascular obstruction in patients with ST-segment elevation myocardial infarction, providing one possible mechanistic link for the association between blood monocyte subsets and myocardial healing.

However, despite great advances in imaging, data on the recruitment behaviour and local distribution of monocytes in human myocardium were still lacking. The histopathological data presented here by van der Laan et al. widely confirm the observations made in mice that there is a spatio-temporal heterogeneity in monocyte subset distribution based on the above-mentioned surface markers, CD14 and CD16. These data are of great importance, especially as differences in murine and human immunology have always to be kept in mind, e.g. many groups and companies are currently trying to find an activator of regulatory T cells to treat, for example, autoimmune diseases. A superagonistic antibody was developed and well characterized in mice and larger animals, including primates. However, the superagonistic antibody had a fatal outcome when tested in six human volunteers in a phase I clinical study. This indicates that even a very deep understanding of the role of immunity in animal disease models and targeted therapeutics tested in different species does not prevent unexpected effects in man, which can produce deleterious side-effects. Furthermore, even if we have human data, the analysis of blood samples for biomarkers, which is becoming increasingly available from large patient cohorts, cannot substitute for tissue analysis for the study of cellular responses to sterile tissue inflammation, especially in myocardial disease. The analysis of circulating leukocytes...
also does not really reflect the recruitment and migratory kinetics of leukocytes after myocardial injury. Therefore, data from human tissue specimens are highly valuable, even when they are merely confirmatory and limited by inevitable factors, such as small sample size and heterogeneous groups studied. For that reason, the integration of knowledge from human data—epidemiological, genetic, as well as biosamples—with molecular biology that describes intracellular signalling in vitro, as well as cellular immunology that monitors leukocyte communication in vivo, should be a focus of a concerted effort in future cardiovascular research.

Heart failure: a systemic disease

In elegant mouse experiments, it was recently shown that the sympathetic nerve system, angiotensin II, and cytokines/chemokines, especially interleukin-1β, regulate proliferation, release from bone marrow and spleen, and migration of leukocytes after myocardial infarction. Indeed, van der Laan et al. could confirm by their post mortem analysis of different tissues that macrophages leave the bone marrow and spleen to infiltrate the ischaemic myocardium (see Figure 1). This indicates that after cardiac ischaemia, appropriate healing depends on the correct co-ordination of different organ systems involving both systemic neuro-humoral activation and immnity. Indeed, this seems to be a common phenomenon in CHF; usually, symptoms and problems of heart failure are not restricted to the heart. Heart failure and its complications concern the whole organism, with stroke, renal failure, anaemia, cerebral dysfunction, and depression as common consequences. At present, it is unclear which molecular and cellular mechanisms might trigger this 'systemic disease' in heart failure. Surprisingly, the molecular pathways and pathophysiological mechanisms for the different diseases seem to be fairly similar. One is therefore tempted to speculate about a common mechanism pathophysiologically connecting the different organ systems.

The activation of the immune system might well be such a linking effector system (see Figure 1), given that all the diseases listed above are modulated by inflammation. For example, even major depression, which is considerably prevalent in heart failure patients and constitutes an independent predictor of mortality, may be caused by inflammation and is adversely affected by inflammation. Thus, a better understanding of the activation, triggers, and course of inflammation may help to improve not only heart failure, but also its systemic consequences, with a major impact on the morbidity and mortality of our CHF patients.

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References

CARDIOVASCULAR FLASHLIGHT

A rare case of multi-chambered fungal endocarditis from a virulent Cunninghamella infection

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A 60-year-old woman with graft-versus-host disease after bone marrow transplantation for myelodysplastic syndrome developed sudden onset of angina with elevated troponins raising suspicion for acute coronary syndrome. A left heart catheterization did not indicate any significant coronary artery disease. A transthoracic echocardiogram (TTE) revealed inferior wall hypokinesis with a large mass within the left ventricular (LV) cavity suggestive of thrombus or endocarditis. A recent TTE done 2 weeks back, however, had not shown any abnormalities. Within 24 h, the patient’s clinical status deteriorated dramatically, requiring emergent intubation and vasopressor support.

The patient was transported to the operating theatre for an emergency surgery for removal of the LV mass. After induction of general anesthesia, baseline transoesophageal echocardiogram (TEE) examination revealed global LV hypokinesis with ejection fraction of 15–20%. An intracavitary LV mass was seen along with a new mass occupying a substantial portion of the Left Ventricle Outflow Tract (LVOT) (Panel A). Turbulence on colour flow Doppler was suggestive of LVOT obstruction (Panel B). Multiple mobile masses that were not present 24 h earlier were now seen attached to the free wall of the right ventricle (Panel C). TEE examination prompted the surgical team to perform a right atriotomy in addition to debridement of the LV via left atriotomy. The immediate pathological evaluation revealed fungal hyphae and later confirmed the diagnosis of a rare Cunninghamella species. Panel D shows H&E stain of fungal hyphae obtained from LV mass (Panel E). Post-operatively the patient succumbed to disseminated intravascular coagulation and died in the intensive care unit within a few hours after surgery.

The rapidity of growth and involvement of multiple chambers could be suggestive of the virulent nature of this rare fungus urging maintenance of high suspicion in immune compromised patients and early administration of antifungal agents. Although epidemiology on geographical distribution is limited, predisposition of this pathogen to patients receiving deferroxamine and the presence around construction areas has been reported.

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