Abstract: 2163

Molecular imaging of cardiac and neuroinflammation early after myocardial infarction and in progressive heart failure

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Background/Introduction: Myocardial infarction (MI) triggers local inflammation to support endogenous healing and repair. Recent imaging studies of the macrophage- and microglia-expressed mitochondrial translocator protein (TSPO) identified concurrent neuroinflammation after acute MI and in chronic heart failure. The source of this neuroinflammation and its relationship to cardiac function early and late after MI are unknown.

Purpose: We aimed to characterize the cellular basis of the TSPO PET signal by modulating early inflammation via clodronate-mediated macrophage depletion, and modifying late mitochondrial function using the TSPO inhibitor PK11195.

Methods: C57BL/6 mice underwent permanent coronary artery ligation (n=47) or sham surgery (n=9). Subgroups were treated 24h prior surgery with clodronate liposomes (n=18) to deplete peripheral macrophages or continuously with the cardioprotective TSPO inhibitor PK11195 (n=13). Cardiac and neuroinflammation were evaluated by whole-body PET using the TSPO ligand 18F-GE180 at 1wk, 4wk and 8wk after surgery. Cardiac function and perfusion were assessed by ECG-gated 99mTc-sestamibi SPECT.

Results: Untreated MI mice showed elevated TSPO signal in the infarct territory compared to sham at 1wk post-MI (ID/g, 10.5±2.9 vs 7.2±1.6, p<0.001), and elevated remote myocardial TSPO signal at 8wk (ID/g, 9±1.9 vs 7±1.6, p=0.003). TSPO signal in brain of MI mice was also increased compared to sham at 1wk (ID/g, 2.1±0.3 vs 1.8±0.2, p=0.006) and 8wk (ID/g, 2.0±0.3 vs 1.8±0.2, p=0.033), reflecting neuroinflammation. Clodronate macrophage depletion lowered the infarct territory TSPO signal at 1wk compared to untreated (ID/g, 4.9±1 vs 10.5±3, p<0.001), consistent with lack of peripheral macrophage recruitment. Conversely, brain TSPO remained elevated (ID/g, 2.7±0.3 vs 2.2±0.3, p=0.001), suggesting resident microglial activation as the source of cerebral PET signal. Late signal at 8wk was comparable between clodronate and untreated (p=NS). TSPO inhibition by PK11195 treatment did not affect acute TSPO signal in heart or brain compared to untreated (p=NS). At 8wk, remote myocardial signal was reduced (ID/g, 7.4±1 vs 9.0±2, p=0.040) in parallel with attenuated cardiac dysfunction in PK11195 treated mice (%EF, 49.8±6 vs 37.3±5, p<0.001). Late brain TSPO signal at 8wk was comparable between PK11195 treatment and untreated (p=NS). Consistently, cardiac and brain TSPO signal were proportional (r=0.637, p<0.001), and neuroinflammation was correlated to cardiac function at 8wk after MI (r=-0.345, p=0.005).

Conclusions: Cardiac TSPO signal reflects acute macrophage activity and chronic mitochondrial dysfunction in heart failure. Neuroinflammation derives from resident microglia, and is proportional to cardiac function at late stages. As such, TSPO PET provides insight into inflammation and mitochondrial dysfunction in progressive heart failure, and may guide novel therapies such as cardioprotection via TSPO inhibition.