

**Uptake of extracellular complement C3 by cardiomyocytes intervenes the intrinsic apoptosis.**

A recycling pathway of complement C3 was discovered as a component of the intracellular complement system. Human immune cells (B and T lymphocytes) and non-immune cells (endothelial cells) can rapidly internalize C3 from the extracellular milieu, which plays an important role in T cell survival and epithelial cell death. We investigated if the uptake of extracellular C3 can take place in the parenchymal cells which shielded by endothelial/epithelia barriers and further studied the pathophysiological role of such internalized C3. Using an in vitro system of human cardiomyocytes, we found that AC-16 cardiomyocytes, which did not produce matured C3, were readily uptake the exogenous C3 once being exposed to it. Such internalized C3 helped these cells to mitigate apoptosis under oxidative stress condition. Cardiomyocytes may be exposed to circulating C3 after the endothelial barrier being compromised, which happened upon the reperfusion of ischemic myocardium. We further investigated in the effect of internalized C3 in an animal model of myocardial ischemia/reperfusion (IR). Our results showed that C3<sup>-/-</sup> mice had significant increase of apoptosis compared with WT mice. Furthermore, C3-bound immunocomplex from WT mice undergone IR contained Cyt c, a key apoptotic factor in the intrinsic apoptosis pathway. Biochemically, C3 purified from blood can inhibit the Cyt c mediated cell death in a cell free apoptosis system. Thus, the C3-uptaking mechanism by the parenchymal cells may serve as an innate immune surveillant for intracellular homeostasis by recognition of potential intracellular damage-associated molecular pattern molecules (DAMPs).