Cardiovascular disease is the leading cause of death in Western countries. A major limitation of current treatments is the inability to efficiently repair or replace dead myocardium. Recently, stem cell-based therapies have been explored as an avenue to circumvent current therapeutic limitations. Overall, these therapies seem to result in small improvements in the contractile function of the heart. The exact mechanism(s) of action that underlie these improvements remain unknown, and it is believed that paracrine effects play a significant role. Previously, we had reported that an extract derived from bone marrow cells, in the absence of any live cell, contained cardioprotective soluble factors. In this study, we identify IL-15 as a putative cardioprotectant within the bone marrow cells paracrine profile. Using an in vitro culture system, we assessed the ability of IL-15 to protect cardiomyocytes under hypoxic conditions. For the first time, we have identified IL-15 receptors on the surface of cardiomyocytes and delineated the signaling system by which hypoxic cardiomyocytes may be protected from cellular death and rescued from oxidative stress with IL-15 treatment.