BET protein inhibition prolongs cardiac transplant survival via enhanced myocardiac autophagy

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Graft rejection remains a major barrier to long-term engraftment after transplantation. Autophagy plays an important role in cardiac ischemia reperfusion and cardiac injury pathogenesis. The bromodomain and extraterminal protein inhibitor JQ1 inhibits inflammatory responses. However, the beneficial effect of JQ1 on transplant tolerance and the potential role of autophagy in the protective effect of graft survival have yet to be investigated. Our study revealed that JQ1 treatment evidently prolonged cardiac allograft survival, but LKB1 deficiency among donors eliminated the tolerogenic effect of JQ1. JQ1 increased the expression levels of LKB1, ATG5, and LC3-II and potentiated the phosphorylation of AMP-activated protein kinase (AMPK), ULK1, and ATG14 in the allografts. A conditional ATG5 deletion donor was utilized to abrogate transplant tolerance induced by JQ1. The combined use of JQ1 with Bafilomycin A1 partially reversed the tolerogenic effect of JQ1, suggesting that autophagy is involved in the signaling pathway in graft survival. JQ1 decreased the frequencies of Th1, Th2, Th17, and regulatory T cells in vitro and downregulated the expression of inflammatory cytokines, such as IL-2, IL-6, IL-1β, TNF-α, IFN-γ, and IL-17, but JQ1 could not prevent CD4+ and CD8+ T cell activation in vivo. Thus, JQ1 prolonged cardiac allograft survival by potentiating myocardiac autophagy through the LKB1-AMPK-ULK1 signaling pathway and inhibiting the subsequent release of inflammatory cytokines. This result might provide novel insights into transplant tolerance induction.

Recent Publications

1. Liu C, Cheng XW, Chen JT, Wang Y, Wu XY, Tian R, Liu BQ, Ding XF, Sun QM*, Gong WH*. Suppression of YAP/TAZ-Notch1-NICD axis by bromodomain and extraterminal protein inhibition impairs liver regeneration. Theranostics. 2019; 9(13): 3840-3852
2. Jin Y, Kong DQ, Liu C, Gong WH*. Role of IL-33 in transplant biology. European Cytokine Network. 2019 Jun 1; 30(2):39-42
3. Chen JT, Liu C, Liu BQ, Kong DQ, Wen L, Gong WH*. Donor IL-6 deficiency evidently reduces memory T cell responses in sensitized transplant recipients. Transpl Immunol. 2018 Dec; 51:66-72
4. Shi XY, Liu C, Liu BQ, Chen JT, Wu XY, Gong WH*. JQ1: a novel potential therapeutic target. Pharmazie. 2018, Sept 1; 73(9):491-493
5. Gong WH*, Liu BQ, Chen JT, Liu C, Shen ZH*. Impact of regulatory T cells on innate immune cells in a presensitized heart transplant model. Annals of Transplantation. 2018 Apr 13; 23:246-251

Biography

Dr. Weihua Gong has completed his PhD at the age of 31 years from Charité-University Medicine Berlin, joint school of Humboldt University and Berlin Free Uinversity and postdoctoral studies from University of California at Los Angeles and Harvard Medical School. He is principal investigator of Zhejiang Univesrity in the field of surgery and transplantation. He has published more than 50 papers in reputed journals and has been serving as an editorial board member of Journal of Translational Medicine and section editor of Current Stem Cell Research & Therapy.

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