Adiponectin Supports Cell Survival in Glucose Deprivation Through the Enhancement of Autophagic Response in Colorectal Cancer Cells

（アディポネクチンはグルコース欠乏状態でのｵｰﾄﾌｧｼﾞｰを増強することにより、大腸癌細胞の生存を助長する）

北山 丈二準教授
東京大学大学院医学系研究科
平成 19 年 4 月入学
医学博士課程
外科学専攻
ベイカー　(シャラル)　ハビーブ

Baker　　(Shalal)　　Habeeb

Abstract

Adiponectin is known to have suppressive effects on tumor growth and is thought to be a key molecule in the positive correlation between obesity and cancer. However, the detailed mechanisms regulating tumor cell activity have not been elucidated. In this study, I found that both full-length (f-Ad) and globular adiponectin (g-Ad) inhibited cell growth in colon cancer cell lines in glucose-containing medium, whereas it supported cell survival in glucose-deprived medium, with an increase in AdipoR1 and AdipoR2 expression. The latter effect of adiponectin in glucose deprivation was significantly inhibited by adding autophagy inhibitors, chloroquine, 3-MA or a combination of pepA and E-64d, suggesting that the effect to support cell growth was dependent, at least in part, on the induction of autophagy. The enhancement of autophagy was confirmed morphologically using GFP-LC3 fusion proteins under a fluorescence microscope using stably transfected DLD-1 cells expressing GFP-LC3. Western blot analysis revealed that

adiponectin increased the expression of LC3-1, LC3-2, phosphorylated AMPKα and PPARα but decreased that of phosphorylated mTOR, IGF-1, phosphorylated Akt and phosphorylated PI3K in glucose-deprived medium. I conclude that adiponectin supports cell survival in glucose deprivation through enhancement of the autophagic machinery by AMPKα and PPARα activation and IGF-1/PI3k/Akt/mTOR pathway inhibition. The bimodal effects of adiponectin are thought to be clinically important in the pathophysiology of tumor development and progression.

Abbreviations:

(AMPK) adenosine monophosphate-activated protein kinase, (mTOR) mammalian target of rapamycin, (f-Ad) full-length adiponectin, (g-Ad) globular adiponectin, (CQ) chloroquine, (pepA) pepstatin A, (3-MA) 3-methyl adenine, (LC3) microtubule-associated protein 1 light chain 3, (GFP) green fluorescent protein, (PPAR) peroxisome proliferator-activated receptor, (IGF-1) insulin like growth factor, (Akt) serine/threonine kinase, (PI3K) Phosphatidylinositol 3-kinase.