**Metformin promotes antitumor immunity via endoplasmic reticulum-associated degradation of PD-L1**

The type 2 diabetes drug, metformin, has been reported to possess antitumor effects and maintain high cytotoxic T lymphocyte (CTL) activity, suggesting that metformin may play a role in immune surveillance. However, the functions and the detailed mechanisms of metformin related to cancer immunity are not fully understood. Here we show that metformin increases CTL activity by reducing the stability and membrane localization of programmed death ligand-1 (PD-L1), one of the key immune checkpoints in cancer immune evasion. The antitumor effect of metformin is significant in immunocompetent but not in immunodeficient mouse model. Furthermore, we discover that AMP-activated protein kinase (AMPK) activated by metformin directly phosphorylates S195 of PD-L1. S195 phosphorylation induces abnormal glycosylation of PD-L1, resulting in its ER accumulation and ER-associated degradation (ERAD). Consistently, tumor tissues from metformin-treated breast cancer patients exhibit reduced levels of PD-L1 with AMPK activation. Blocking the inhibitory signal of PD-L1 by metformin enhances CTL activity against cancer cells. Our findings identify a new regulatory mechanism of PD-L1 expression through the ERAD pathway and suggest that the combination of metformin and CTLA4 blockade has the potential to increase the efficacy of immunotherapy.