Human leukocyte antigen-G (HLA-G) has been identified as an immune checkpoint receptor (ICP) and a neo-expressed tumor-associated antigen (TAA) in a large proportion of solid tumors.

Chen et al. evaluated the induction of HLA-G as well as PD-L1 by sub-lethal doses of chemotherapeutics including pemetrexed in different NSCLC cell lines. Except for gefitinib, most of the chemotherapeutic agents enhanced HLA-G and PD-L1 expression in a dose-dependent manner, whereas pemetrexed and carboplatin treatments showed the most consistent upregulation of PD-L1 and HLA-G in each cell line. In addition to protein levels, a novel finding of this study is that pemetrexed enhanced the glycosylation of HLA-G and PD-L1. Pemetrexed potentiated the cytotoxicity of cytotoxic T lymphocytes (CTLs) to treat NSCLC. Both in vitro and in vivo experiments revealed that the CTL-mediated cytotoxicity was most pronounced when both anti-PD-L1 and anti-HLA-G ICBs were combined with pemetrexed treatment. In conclusion, anti-HLA-G could be an intervention strategy in addition to the anti-PD-1/PD-L1 pathway for NSCLC. Moreover, dual targeting of PD-L1 and HLA-G combined with pemetrexed may have a better extent of CTLs-based immunotherapy [1].

1)
Chen MC, Hung MY, Pan CM, Huang SW, Jan CI, Li YH, Chiu SC, Cho DY. Pemetrexed combined with dual immune checkpoint blockade enhances cytotoxic T lymphocytes against lung cancer. Cancer Sci. 2023 Apr 5. doi: 10.1111/cas.15806. Epub ahead of print. PMID: 37017116.