CD274 (PD-L1)-Expression in colorectal cancer

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EDITORIAL

Immunotherapy targeting immune checkpoint has emerged as a promising therapeutic strategy against cancer (1). Aberrantly expressed CD274 (programmed cell death ligand 1, PD-L1) on tumour cells was reported to down-regulate T-cell-mediated immunity and help immune evasion of tumour cells (1). Therapeutic antibodies targeting CD274/PD-1 (programmed cell death 1, PD-1) axis are effective for treating distinct types of tumours (1,2). Immunohistochemistry for CD274 has been suggested as a potential biomarker to predict efficacies of anti-CD274/PD-1 checkpoint inhibitors (2). Under these circumstances, several research groups, including us, has attempted to uncover the clinicopathologic profile, immunophenotype and genotype of CD274-positive colorectal carcinomas (CRCs) (3-7). In addition to the histopathological and genetical analyses, our group tried to uncover CD274-regulation mechanism(s) using cultured CRC cells (7).

In primary CRCs, approximately 15% of cases are believed to develop through the serrated neoplasia pathway, showing mucinous and/or poorly differentiated/medullary histology, mismatch repair-deficiency or “stem-like” immunophenotype in metastatic CRCs (1-3). In several types of cancers such as lung cancer, breast carcinoma, and renal cell carcinoma, recent studies have shown intratumour heterogeneity or differential expression of CD274 in isogenic primary and metastatic tumours (11-13). Hence, we analyzed 189 metastatic CRCs for CD274 expression and found that about 14% of metastatic CRCs showed cytoplasm-dominant CD274 expression (7). Unlike primary tumours, this attempt showed no clear association between CD274 expression and tumour intrinsic factors such as MMR-deficiency or “stem-like” immunophenotype in metastatic CRCs (7). Furthermore, gene mutation analyses revealed common KRAS mutations (54%) in CD274-positive metastatic CRCs (7). These results indicate that epigenetic mechanisms, such as tumour microenvironmental factors, might dominantly regulate CD274 expression in metastases.

Based on these results, we tested interferon-γ (IFNγ) and transforming growth factor-β1 (TGF-β1) famous soluble factors secreted from stromal cells, for CD274 regulation in five colon cancer cell lines. As a result, all of the cell lines were responsive to exogenous IFNγ for CD274 up-regulation through JAKSTAT pathway, regardless of their subtypes such as MMR-deficiency or “stem-like” immunophenotype in metastatic CRCs (7). These experimental results suggest that IFNγ regulates CD274 expression in CRC cells. Further molecular biological studies are needed to understand a complicated CD274 regulating mechanism in CRCs.

In summary, recent studies have identified significantly distinct characteristics in CD274-positive primary and metastatic CRCs. Immunohistochemical evaluation of metastases should be considered in planning CD274/PD-1 axis inhibitors therapy so that non-optimal use of the drugs would be avoided. Further molecular biological studies are needed to understand a complicated CD274 regulating mechanism in CRCs.

CONFLICT OF INTEREST

The author has disclosed no relationships with, or financial interest in, any commercial companies pertaining to this article.

REFERENCES
