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/PDCD1 (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/PDCD1 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 (MMR)-deficiency, mutational BRAF activation, and CpG island methylator phenotype (8-10). Several studies have identified significant associations between CD274 expression and characteristics of serrated neoplasia pathway-driven CRCs (3,5,6). Further immunohitochemical characterization of CD274-positive primary CRCs has revealed "stem-like" immunophenotype defined by down-regulation of CDX2 (Caudal-type homeobox transcription factor 2), an intestinal differentiation marker and membranous expression of a stem cell marker ALCAM (activated leukocyte cell adhesion molecule, CD166) (3). Experimental confirmation for "stemness" of CD274-positive CRC cells has, however, never been performed.

In several types of cancers such as lung cancer, breast carcinoma, and renal cell carcinoma, recent studies have showed intra-tumour 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 cytoplasms-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 micro environmental factor(s), 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 INFγ for CD274 up-regulation through JAK-STAT pathway, regardless of their subtypes such as MMR-deficiency or RAS/BRAF mutation status. On the other hand, CD274 regulation by TGF-β1 varied: up-regulation, down-regulation, and no clear change (7). These experimental results suggest that INFγ and/or TGF-β1 within tumour micro environment could modulate CD274 expression.

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/PDCD1 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.

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