In Focus
4th Immunotherapy of Cancer Conference (ITOC4), March 20–22, 2017, Prague, Czech Republic

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1. Targeting CCR5 for Macrophage Repolarization in Cancer Immunotherapy

Colorectal cancer is a devastating disease, especially for patients with unresectable metastatic lesions. Niels Halama (Heidelberg, Germany) and colleagues set out to investigate the local immunological microenvironment in colorectal cancer liver metastases. With a sophisticated approach utilizing whole slide image quantification and multiplex proteomics, the spatial profile revealed an unexpected relationship between lymphocytes and tumor cells. Further experiments showed a tumor-promoting role for CD4+ and CD8+ T lymphocytes in metastatic colorectal cancer that directly elicit proliferation and production of pro-tumorigenic inflammatory cytokines mediated by the chemokine axis CCL5-CCR5. Tumor promotion is induced by enhanced migratory properties of tumor cells and pro-metastatic factors produced by tumor-associated macrophages. A newly developed fully human tumor explant model system allowed systematic functional characterization and showed effective abrogation of this pathomechanism by a selective CCR5 inhibitor. Blocking CCR5 leads to antitumoral repolarization of macrophages in the microenvironment. Translation into a clinical trial with advanced metastatic colorectal cancer patients confirmed the therapeutic efficacy of CCR5 blockade, especially in mitigating this pro-tumor inflammatory microenvironment through effects on both tumor cells and tumor-associated macrophages. This prospective trial also validated the predictions of the explant model system and therefore highlights the possibilities of this strategy for translational research.

2. Tumor Cell-intrinsic Signaling Affects Antitumor Immune Responses

While immunotherapy has been shown to be effective in many types of cancer, only a fraction of patients is responding within each cancer type. Clinical data have indicated that efficacy of immune checkpoint blockade is associated with a T-cell-inflamed tumor microenvironment phenotype at baseline. Stefani Spranger (Chicago, USA) and colleagues investigated whether tumor cell-intrinsic signaling pathways might dominantly impair local T-cell infiltration and identified Wnt/β-catenin signaling as the first pathway directly impacting T-cell infiltration. By using genetically engineered melanoma (GEM) mouse models, the researchers identified that activation of β-catenin signaling inhibits productive T-cell priming. They also showed that β-catenin signaling mediates secondary resistance to circulating effector T cells, generated either by immunization or adoptive T-cell transfer. Intra-vital microscopy revealed that effector T cells in β-catenin-negative tumors showed directed migratory behavior and made close tumor cell contacts, while the few T cells in β-catenin-positive tumors failed to make contact with tumor cells. Mechanistically, the researchers identified CD103 dendritic cells (DCs) as the source for the chemokines CXCL9/10 in β-catenin-negative tumors, while β-catenin-positive tumors lacked this DC subtype and therefore failed to recruit effector T cells. The findings support the notion that CD103 DCs within the tumor microenvironment are essential for effector CD8 T-cell recruitment, and that recruitment of CD103 DCs might enhance checkpoint blockade efficacy.

3. DRibbles Vaccine Exploits Autophagy to Boost Antitumor Immune Responses

David B. Page (Medford, USA) and colleagues have developed a novel multi-valent vaccine platform called DRibbles, which is comprised of autophagosome-packaged cellular proteins, short-lived proteins and ribosomal proteins. These proteins can be tumor-associated antigens, mediators of innate immunity, surface markers that encourage phagocytosis and cross-presentation by antigen-presenting cells (APCs), and molecules such as CLEC9a ligand that encourage uptake of DRibbles by cross-presenting APCs. The first proof-of-principle DRibbles vaccine, DPV-001, is derived from two non-small cell lung carcinoma (NSCLC) cell lines, and contains over 2000 proteins, of which 25 are known tumor-associated antigens. Autologous DRibbles vaccine has been shown to be well tolerated in a Phase 1 trial in NSCLC patients when combined with docetaxel plus GM-CSF, and several other trials are ongoing. The DRibbles platform can be used to create autologous or allogeneic vaccines across a broad range of cancer types. Compared to peptide and DNA vaccines, the DRibbles autophagosome-enriched vaccine platform may serve to immunize against a broad spectrum of antigen types including potential neo-epitopes and a short-lived/defective cellular proteins that may not be present in other complex cell-derived cancer vaccines.

4. Transcriptomic and Phenotypic Differences of Immune Cells in Breast Cancer Patients

Despite advances in early diagnosis and treatment, breast cancer recurrence rate remains high. Stephanie E. Mc Ardle (Nottingham, UK) and colleagues examined the profile of Treg, myeloid-derived suppressor cell (MDSC), monocyte and NK cell subsets in the peripheral blood of...
breast cancer patients. They found significantly increased levels of circulating Treg cells and MDSCs in cancer patients, and levels positively correlated with tumor burden. Treg cells from patients displayed a more suppressive/activated phenotype. The percentage of HLA-DR<sup>−</sup>CD11b<sup>+</sup>CD33<sup>+</sup> cells expressing CD15 was also greater in patients. In addition, levels of ‘classical’ monocytes (CD14<sup>+</sup>CD16<sup>−</sup>) were lower, but levels of ‘intermediate’ monocytes (CD14<sup>+</sup>CD16<sup>+</sup>) were significantly higher in patients, with the differences correlating with disease stage. Phenotypic profiles strongly correlated with transcriptomic data. Anthracycline chemotherapy induced a significant decrease in total B-cell count and increase in monocyte count, but had no effect on Treg and MDSC numbers. Chemotherapy also had no effect on NK cell count, but induced an increase in the expression of inhibitory receptors, and a decrease in the expression of activating receptors. Phenotypic profiling and immune gene transcript analysis of peripheral blood mononuclear cells have the potential to inform clinical decision and help to predict therapeutic response.