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Meeting report

Innovative Therapy, Monoclonal Antibodies and Beyond

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ABSTRACT

The seventh Edition of “Innovative Therapy, Monoclonal Antibodies and Beyond” Meeting took place in Milan, Italy, on January 27, 2017. The two sessions of the meeting were focused on: 1) Preclinical assays and novel biotargets; and 2) monoclonal antibodies, cell therapies and targeted molecules. Between these two sessions, a lecture entitled “HLA-antigens modulation and response to immune checkpoint inhibitor immunotherapy” was also presented. Despite the impressive successes in cancer immunotherapy in recent years, the response to immune based interventions occurs only in a minority of patients (~20%). Several basic and translational mechanisms of resistance to immune checkpoint blockers (ICBs) were discussed during the meeting: 1. the impact of tumor microenvironment on the activity of immune system; 2. strategies to inhibit the cross-talk between extracellular matrix and myeloid-derived suppressor cells (MDSC) in the preclinical setting; 3. microRNA expression as a biomarker and as a target of therapy in non-small cell lung cancer (NSCLC); 4. the significance of complement activation pathways in response to immune checkpoint inhibitors; 5. the immunosuppressive activity of the microbiota by inducing IL-17 producing cells; and 6. modulation of HLA antigens as possible markers of response to ICB therapy. In order to overcome the deficiency in active anti-tumor T cells, several clinically applicable combination strategies were also discussed: 1. strategies to enhance the anticancer effects of immunogenic cell death inducing-chemotherapy; 2. the use of CAR T-cells in solid tumors; 3. the use of combination strategies involving oncolytic viruses and ICBs; 4. combinations of new ICBs with anti-PD-1/CTLA-4 therapy; and 4. combinations of targeted therapies and ICBs in melanoma. Overall, this conference emphasized the many novel strategies that are being investigated to improve the overall patient response to cancer immunotherapy. Optimization of biomarkers to accurately select patients who will respond to immunotherapy, coupled with combination strategies to improve long term patient survival remain critical challenges in the immuno-oncology field.

1. Introduction

The 7th edition of the Conference “Innovative Therapy, Monoclonal Antibodies and Beyond” was held at the Fondazione IRCCS Istituto Nazionale Tumori, Milan Italy on January 27, 2017. The conference brought together leading international experts in the field of immuno-oncology and cancer cell signaling with the goal to understand the potentials, opportunities and challenges in the rapidly moving field of cancer immunotherapy and targeted therapies.

The key role of the immune system in cancer control has long been recognized, but the development of clinically effective immune strategies has fundamentally changed the nature of cancer treatment. Indeed, an improved understanding of the co-evolution of cancer and immune system, the molecular mechanisms responsible for neoplastic

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transformation, and the immunological mechanisms regulating tumor-host interaction, has permitted the application of new highly effective immunological and biological anti-cancer treatments. Cancer bio-immunotherapy is now effectively integrated into the treatment algorithms of different tumor types such as melanoma and lung cancer. Further elucidation of cancer-related resistance mechanisms and sensitivity to therapeutics will continue to contribute to improve cancer therapy and patient care.

The “Innovative Therapy, Monoclonal Antibodies and Beyond” conference explored several topics that appeal to clinicians, as well as basic and translational scientists in academia and industry. As in the past, the meeting provided a highly interactive forum in which leading experts discussed pre-clinical and clinical data, providing the audience with a broad overview of the recent achievements in cancer biological and immunological therapies. Finally, encouraging new data supporting the combination of immunotherapy with current standard of care treatments offers an intriguing opportunity, as well as challenge for future therapeutic developments. In the following sections, we offer a summary of the plenary lectures from the conference that span research from the bench to the bedside and back again.

2. Preclinical and translational features

2.1. Role of ECM in the tumor host crosstalk

Transformed tissues communicate with immune cells within the tumor environment, resulting in functional cross-talk and tissue remodeling imposed by the growing tumor. Mast cells (MC) are granulocytic immune cells with an important role in allergy and anaphylaxis, as well as important functions in innate immunity against bacteria, viruses, and parasites. MCs are also found aggregated around and within many solid cancers, with roles in fostering angiogenesis, tissue remodeling, and immunomodulation in human and murine cancer. In previous studies, MP Colombo and colleagues (Fondazione IRCCS Istituto Nazionale Tumori, Milan) demonstrated that MC are essential players in the initial stages of prostate tumor progression by supplying matrix metalloprotease 9 (MMP-9) to break down the basal membrane layers; however, MC become dispensable at later, post–epithelial-to-mesenchymal transition (EMT) stages. Strikingly, ablation of MC in Transgenic Adenocarcoma Mouse Prostate (TRAMP) mice, either genetically or pharmacologically, reduced the number of mice developing adenocarcinoma, but favored the development of mice with early neuroendocrine tumors (NE) [1]. Oncogene transformation of the basal cell layer in the NE tumors was shown to be dependent on osteopontin (OPN) produced by MC. Furthermore, animals depleted for MC, or TRAMP mice deficient in OPN expression, developed NE lesions [2]. These data suggest that the same oncogene, the SV40 Large T antigen can generate tumors of different and prevalent histotypes, depending on the presence/absence of mast cells or OPN.

The depletion of another matricellular protein – Secreted Protein Acid and Rich in Cysteine (SPARC) – also plays a role in transformation. The transition from an autoimmune state, due to Fas deficiency, and proliferation of self-reactive double negative $CD3^+$ $B220^+$ lymphocytes leads to a B1 neoplasm resembling CLL. Such neoplastic transition is promoted by the downregulation of collagen, the assembly of which depends on SPARC. The collagen receptor LAIR-1, endowed with an inhibitory ITIM motif with suppressive capacity, is expressed by activated PMNs; in the absence of collagen, PMN became hyper-activated toward a particular form of cell death termed NETosis. Neutrophil extracellular traps (NETs) are threads of neutrophil DNA decorated with cytoplasmic protein that are extruded by neutrophils to neutralize certain pathogens. Such NETs are immunogenic and can trigger a lupus-like disease; moreover neutrophils undergoing NETosis release B cell growth factors BAFF and IL-21. The encounter between neutrophils and B lymphocytes in secondary lymphoid organs is normally restricted by the collagen scaffold, with neutrophils confined to the marginal zone of the lymph node. In contrast, neutrophils that do not express collagen are no longer localized to the marginal zone. Thus, the absence of SPARC and collagen permit close interactions between NETting neutrophils and B1 lymphocyte, leading to transformation under the autoimmune conditions of a Fas deficient background [3]. Similarly, the spleen from human CLL displayed a NET-like structure when immunostained with myeloperoxidase in the context of low SPARC and collagen [3]. Altogether, these observations − in mice and in patient samples − indicate that certain disease manifestations may require either OPN or SPARC downregulation.

2.2. Microbiota and immune response

It has long been recognized that the human body is composed not only of eukaryotic cells, but also of colonizing microrganisms (collectively referred to as the microbiota) [4], in a ratio estimated to be in the range of 1:1.3 [5]. Indeed, the microbiota fully contributes to human health by providing essential nutrients, protecting against pathogens, and by educating the immune response. More recently, evidence has accumulated that the delicate balance between commensal bacteria and the immune system is essential to the maintenance of tissue integrity throughout the body, not just in the aerodigestive tract. Dysbiosis (i.e., alteration in the normal composition of the microbiome due to the disruption of the intimate relationship between the host and the microbiota) can be triggered by host-derived and environmental factors, including age, morbidities, psychological and physical stress, diet, toxins, drugs and pathogens. As an example, genome-wide analyses have shown that the microbiota may influence host genome expression by regulating miRNA [6], and in turn, host-derived miRNA influences the composition of the gut microbiome [7]. The majority of miRNA decrease with age [8], in part explaining the age-associated modification in the composition of the gut microbiome. Thus, dysbiosis has been correlated with the pathogenesis of both mucosal and extra-mucosal immune-mediated disorders, including inflammatory bowel disease, diabetes, multiple sclerosis, and rheumatoid arthritis [9]. Despite early evidence that antimicrobial therapy prevented solid tumor development in mice [10], less is known about the potential pathogenic role of dysbiosis in cancer. It is now well established that the gut flora participates in intestinal carcinogenesis via production of toxic metabolites, alteration of epithelial cell proliferation and death, and promotion of chronic inflammation and/or local immune suppression, eventually driving mucosal inflammation [11]. While several reports have linked gut microbes with extra-intestinal tumors, including hepatocellular carcinoma [12,13] and breast cancer [14], the cellular and molecular mechanisms by which non-pathogenic microbes drive non-aerodigestive tract malignancies remain to be elucidated [15].

In order to investigate a potential link between the gut microbioma, the immune system and a non-aerodigestive tract malignancy, Matteo Bellone and his group (IRCSS San Raffaele Scientific Institute, Milan) studied the appearance of multiple myeloma (MM) and its progression in Vk*MYC transgenic mice [16]. These mice develop a disease mimicking MM, that as in humans [17], is preceded by an asymptomatic phase [18]. Interestingly, the progression from asymptomatic to symptomatic MM in Vk*MYC mice is characterized by substantial modifications of the bone marrow microenvironment in which disease develops, including a switch from a Th1 to a Th2 response, and accumulation of pro-angiogenic macrophages [18]; these observations suggest a contribution of the immune response to cancer progression in this model. The investigators noticed a different disease behavior in Vk*MYC mice housed in two distant animal facilities. Despite a similar diet, mice in the two animal shelters displayed differences in the composition of the gut microbiome, and these differences were associated with substantial modifications in the bone marrow immune infiltrate. A direct link between gut microbiota and MM was suggested by the fact that antibiotic treatment prevented disease progression in mice transplanted with Vk*MYC tumor cells [19]. In more advanced phases