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Session 5: T-Cellular Responses

Thursday 15th April 2010. Moderators: Jon Sprent and Charlie Surh

[08.30–09.00]

'Antibody-cytokine complexes induce potent and selective immune stimulation'

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Cytokine immunotherapy is a promising approach for the treatment of metastatic cancer and chronic virus infections. Recently, association of the cytokine interleukin (IL)-2 with particular anti-IL-2 monoclonal antibodies (mAb) has been shown to result in the formation of IL-2/anti-IL-2 mAb (IL-2/mAb) complexes, which displayed 30–40-fold increased in vivo activities as compared to IL-2 alone [1]. Moreover, depending on the anti-IL-2 mAb used, IL-2 either preferentially stimulated cells expressing high levels of IL-2 receptor β (CD122) or cells carrying high levels of IL-2 receptor α (CD25). Thus, CD122-directed IL-2/mAb$_{CD122}$ complexes, generated using anti-mouse IL-2 mAb S4B6 or anti-human IL-2 mAb MAB602, induced vigorous expansion of CD122^{high} effector cells such as CD8$^+$ T cells and natural killer cells [1], which mediated potent anti-tumor responses in vivo. Conversely, use of anti-mouse IL-2 mAb JES6-1 or anti-human IL-2 mAb 5344 together with IL-2 resulted in CD25-directed IL-2/mAb$_{CD25}$ complexes [1,2], which led to selective expansion of CD4$^+$ T regulatory cells, thus favorably influencing autoimmune disease in a mouse model of multiple sclerosis and long-term acceptance of allografts [3]. The mechanism of action of IL-2/mAb$_{CD25}$ complexes depended mainly on the presence of neonatal Fc receptors (FcRn), whereas IL-2/mAb$_{CD122}$ complexes relied on FcRn molecules and also conferred anti-IL-2 mAb-mediated protection of IL-2 from binding to CD25 molecules [2]. Apart from IL-2, stimulatory cytokine/mAb complexes could also be formed using IL-3, IL-4, IL-6, and IL-7 [1,4]. Collectively, cytokine/mAb complexes are superior to cytokine alone and might thus be considered for clinical applications.

References

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[09.00–09.30]

'Cytokines and the immune response'

Jon Sprent
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Abstract not provided.

[09.30–10.00]

'Anti-tumor properties of T-cell receptor mimic monoclonal antibodies'

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Monoclonal antibodies (mAb) for cancer treatment are presently in widespread use, demonstrating an effective therapeutic strategy. However, only a limited number of tumor-specific markers expressed uniquely by tumor cells have been discovered, restricting the growth of mAb therapy against cancer. Tumorogenesis is driven by cellular modifications, and some changes provide reliable biomarkers specific for disease conditions. The intracellular localization of many potential targets means poor access to mAb therapy. Further, the molecular nature of most targets re-

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duces the discriminatory potential for small molecule drug agents. In contrast, many of the cellular protein changes associated with disease are sampled by the action of the major histocompatibility complex (MHC) system. The MHC system represents a non-biased proteome-scanning chip, unveiling intracellular changes in protein processing via presentation of peptides on the cell surface. In recent years, mAb have been described for the direct detection and visualization of specific MHC/peptide complexes on the surface of cells. Several groups including ours have consistently generated anti-MHC/peptide mAb. Our approach combines immunization with synthetic complexes and high-throughput screening techniques to create anti-MHC/peptide reagents, which we refer to as T cell receptor mimic (TCRm) mAb. The majority of the TCRm mAb generated using our process have shown high binding affinity, fine binding specificity and can be used for detecting and quantitating specific class I MHC/peptide complexes. We have published our findings that show TCRm recognize MHC molecules bound to disease-specific peptides suggesting that TCRm mAb may offer a novel platform for treating cancer. Our major findings to date establish: (i) a target discovery and validation strategy to identify markers specific for diseased cells, (ii) the disease-exclusive presence of MHC-peptide biomarkers on human tumors, (iii) efficacy of TCRm in several *in vivo* breast tumor models and (iv) a novel mechanism for direct tumor cell killing by TCRm. In this presentation we will describe new findings from pre-clinical models demonstrating the potent anti-tumor activities of TCRm mAb.