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Bridging the gap between animal models and clinical trials: the use of in vitro assays to accelerate cancer immunotherapy development

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During the last years, significant advancement has been made in the clinical application of cancer immunotherapies. Molecules directed against immune checkpoints and other agonists show great promise for treatment of a variety of malignancies. Next to CTLA-4 and PD-1 blockade, a wide range of therapeutics with the potential to reverse the tumor-induced suppression are under development. Early evaluation of the effectiveness of candidate therapeutics and combination therapies can be done using mouse models and in vitro bioassays with human immune cells. Mixed lymphocyte reaction assays using both innate cells and lymphoid cells mimic a real physiological T cell response and are widely used for the potency screening of candidate therapeutics. The use of different allogenic donor combinations can provide additional information on the profile of the responding population. An important factor for sensitive assays and consistent results is the quality of the primary immune cells. PBMC are isolated and cryopreserved shortly after blood redrawn. All donor preparations are quality controlled and HLA typed and optimized procedures are used to generate functional dendritic cells which are co-cultured with allogenic T cells. Response levels can be evaluated by the assessment of proliferation or measurement of cytokine production. Next to the MLR assay, other T cell assays such as antigen-specific recall activation assays can be used to evaluate the ability of test molecules to promote T cell responses. In addition to T cell assays, macrophage polarization assays are an essential tool to evaluate metabolic or other reprogramming functions of test compounds.

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Projected role of modified-albumin in cancer

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Statement of purpose: Extensive research till date suggests that oxidative stress, chronic inflammation, and cancer are closely linked. Inflammation results in the production of numerous reactive oxygen, nitrogen and chlorine species, in addition to the products of lipid and sugar oxidation, some of these products are capable of chemically modifying amino acids in proteins. This in turn results in changes to the structure and function of proteins. Increasing evidence demonstrates that such post-translational modifications result in the generation of neo-epitopes capable of eliciting both innate and adaptive immune responses. Therefore, this study has analyzed the changes in human serum albumin upon modification with peroxynitrite, an endogenously produced powerful oxidizing and nitrating agent, and is implication in the etiopathogenesis of cancer.

Methodology & Theoretical Orientation: Various physico-chemical studies were carried out to establish the modification of albumin. Peroxynitrite-modified-albumin exhibited hyperchromicity at 278 nm, changed microenvironment of tyrosine, tryptophan along with the generation of 3-nitrotyrosine, nitrotryptophan and protein carbonyls.

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