

The role of NFATc1 in T cell-mediated immune responses during the development of lung cancer

Lisanne Heim^{a,*}, Juliane Friedrich^a, Marina Engelhardt^a, Denis I. Trufa^b, Carol I. Geppert^c, Ralf J. Rieker^c, Horia Sirbu^b, Susetta Finotto*

^a Universitätsklinikum Erlangen - Molekulare Pneumologie, Erlangen, Deutschland

^b Universitätsklinikum Erlangen - Thoraxchirurgische Abteilung, Erlangen, Deutschland

^c Universitätsklinikum Erlangen - Pathologie, Erlangen, Deutschland

* Corresponding author, email: susetta.neurath-finotto@uk-erlangen.de

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Purpose/Objectives: NFATc1 (nuclear factor of activated T cells 1) belongs to the NFAT family of transcription factors and regulates T cell activation as well as effector and cytotoxic T cell functions in many tissues. In most of the established tumors, inhibitory receptors like programmed cell death protein 1 (PD-1) contribute to the functional impairment of T cell activation by persistent tumour antigen challenge, a process that is called T cell exhaustion. Cancer immunotherapies are aimed to reawake exhausted T cells by blocking inhibitory checkpoint receptors or immunosuppressive cells. As NFATc1 is important for T cell activation we asked whether this factor could be important for the reactivation of exhausted T cells in non-small cell lung cancer (NSCLC).

Materials/Methods: We analyzed NFATc1 and its interplay with PD-1 in a human NSCLC patient cohort using qPCR, IHC and FACS. Furthermore, in a murine model of lung adenocarcinoma, we determined lung tumour growth in mice with a conditional inactivation of NFATc1 in T cells (NFATc1 Δ CD4) and analyzed the influence of anti-PD-1 antibody treatment on NFATc1 protein levels in T cells of lung-tumour bearing wild-type mice.

Results and Conclusion: In this study, we report a progressive decrease of NFATc1 in lung tumor tissue and in tumor-infiltrating lymphocytes (TIL) of patients suffering from advanced-stage NSCLC. NFATc1 Δ CD4 mice showed increased lung tumor growth associated with impaired T-cell activation and function. Furthermore, in the absence of NFATc1, reduced IL2 influenced the development of memory CD8⁺ T cells. Specifically, we discovered a reduction in effector memory and CD103⁺ tissue-resident memory (TRM) CD8⁺ T cell numbers in the lung of tumor-bearing NFATc1 Δ CD4, underlining an impaired cytotoxic T-cell response and a reduced TRM tissue-homing capacity. Targeting PD-1 resulted in NFATc1 induction in CD4⁺ and CD8⁺ T cells in tumor-bearing mice and was associated with increased antitumor cytotoxic functions. Thus this study reveals a role of NFATc1 in the activation and cytotoxic

functions of T cells, in the development of memory CD8+ T-cell subsets, and in the regulation of T-cell exhaustion. These data underline the indispensability of NFATc1 for successful antitumor immune responses in patients with NSCLC.