LABORATORY OF

IMMUNOLOGICAL AND TUMOUR MODELS

Experimental cancer therapy, tumour immunology, murine models, JAK/STAT signalling, cellular senescence

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more information

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Research

Our long-term research interest are interactions between tumour cells and the immune system, as well as the impacts of anti-tumour therapies on these interactions. We are focused on experimental anti-tumour therapy, using murine models and investigating chemo- and immunotherapies and their combinations. We also pay attention to the mechanisms by which tumour cells can escape from specific immune responses, as well as to the mechanisms of immune suppression development in the tumour microenvironment (e.g., myeloid-derived suppressor cells; [**Fig. 1**]. At present, we concentrate on the impacts of genotoxic stress and cellular senescence induction by chemotherapeutic agents or cytokines and on mutual interactions between stressed/senescent cells and the immune system [**Fig. 2**]. We hypothesize that, despite the fact that cellular senescence represents an important barrier against cancer development, the presence of senescent cells or cells in genotoxic stress in general can influence the development of age-related diseases, and also cancer. Thus not only senescence induction, but also elimination of the effects of these cells are important for effective anti-cancer therapy. The JAK/STAT signalling pathways play important roles in the processes mentioned above. Recently, we have concentrated on the role of STAT1 in cellular stress/senescence induction. Further, we suppose that the STAT3 signalling pathway inhibition can be an important tool for elimination of the negative effects of chemotherapy, and it can also increase its efficacy. Therefore, we study novel and existing STAT3 inhibitors and their potential clinical usage in murine preclinical models.

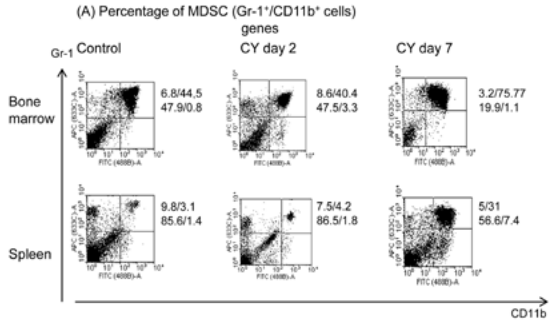

Figure 1. Cyclophosphamide increased the percentage of CD11b+/Gr-1+ cells in the spleens and bone marrow of treated animals.
Bone marrow and spleen after administration of cyclophosphamide (CY), 200 mg/kg i.p. C57Bl/6 mice were injected with 200 mg/kg i.p. and their spleens and bone marrow cells were analysed by flow cytometry 2 and 7 days after injection. Myeloid-derived suppressor cells in the spleen were detected as CD11b+/Gr-1+ cells.

Contractual research and services

We perform analyses of the experimental tumour development and anti-tumour immune responses and we test the efficacy of experimental therapies (not only immunotherapy). We use both tumours induced by syngeneic tumour cell transplantation and transgenic mice as orthotopic models that develop spontaneous tumours. We routinely use experimental models of minimal residual tumour disease after surgery or chemotherapy. Indeed, we are open to more future collaborations and contractual research.

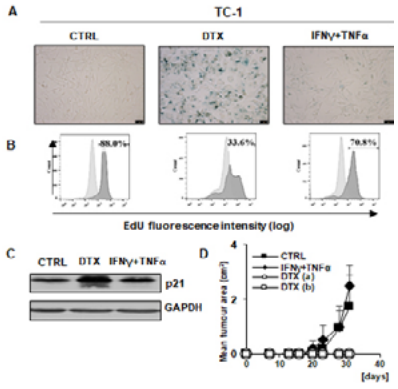

Figure 2. Docetaxel (DTX) but not IFNγ+TNFα induces senescence in TC-1 cells. Senescence-associated β-galactosidase activity in TC-1 cells (A) treated with DTX or IFNγ+TNFα for 4 days. (B) Cell proliferation block after the DTX treatment was detected by 5-Ethynyl-2′-deoxyuridine (EdU), using flow cytometry analysis. Western blot quantification of p21 in control, DTX-, IFNγ+TNFα-treated TC-1 cells (C). Docetaxel-treated TC-1 senescent cells, unlike the IFNγ+TNFα-treated cells or untreated cells (3x104 cells were transplanted s.c.), do not form tumours in mice (D). Mice were injected either with 3x104 or with 3x105 docetaxel-treated cells (DTX (a) and DTX (b), respectively).

Selected publications:

1. Mikyskova R, Indrova M, Stepanek I, Kanchev I, Bieblova J, Vosahlikova S, Moserova I, Truxova I, Fucikova J, Bartunkova J, Spisek R, Sedlacek R, Reinis M* (2017) Dendritic cells pulsed with tumor cells killed by high hydrostatic pressure inhibit prostate tumor growth in TRAMP mice. *Oncoimmunology*, **6**:e1362528.
2. Mikyšková R, Štěpánek I, Indrová M, Bieblová J, Šímová J, Truxová I, Moserová I, Fučíková J, Bartůňková J, Špíšek R, Reiniš M* (2016) Dendritic cells pulsed with tumor cells killed by high hydrostatic pressure induce strong immune responses and display therapeutic effects both in murine TC-1 and TRAMP-C2 tumors when combined with docetaxel chemotherapy. *Int J Oncol*, **48**:953-964.
3. Hubackova S, Kucerova A, Michlits G, Kyjacova L, Reinis M, Korolov O, Bartek J*, Hodny Z* (2016) IFNγ induces oxidative stress, DNA damage and tumor cell senescence via TGFβ/SMAD signaling-dependent induction of Nox4 and suppression of ANT2. *Oncogene*, **35**:1236-1249.
4. Sapega O, Mikyšková R, Bieblová J, Mrázková B, Hodný Z, Reiniš M* (2018) Distinct phenotypes and 'bystander' effects of senescent tumour cells induced by docetaxel or immunomodulatory cytokines. *Int J Oncol*, **53**:1997-2009.

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