**Alpha‐melanocyte‐stimulating hormone and its impact on MDSC generation in skin cancer**

The skin‐derived neuropeptide alpha‐melanocyte‐stimulating hormone (α‐MSH) is a potent immunomodulator that increases the numbers of cytotoxic CD8+ T lymphocytes (CTL) in tumor‐ bearing mice and in samples from human subjects with malignant melanoma (MM). To better understand this process, we investigated the effects of α‐MSH on tumor progression and on anti‐tumoral immunity in a murine carcinogenesis model. Interestingly, mice injected with α‐MSH developed significantly fewer skin tumors than controls and showed increased frequencies of tumor‐specific CTL compared to PBS‐treated controls. Since in the tumor micro‐ environment, the expansion and function of CTL can be controlled by immunosuppressive myeloid‐derived suppressor cells (MDSC), we quantified MDSC levels and demonstrated that α‐ MSH prevented the expansion of this cellsubset. The effect was dependent on binding of α‐MSH to the melanocortin‐1 receptor (MC‐1R) because mice lacking a functional MC‐1R showed normal MDSC and CTL levels as well as a normal tumor development. Hence, we provided evidence that in mouse models of skin cancer α‐MSH regulates anti‐tumoral immunity by preventing the induction of MDSC, which leads to increased levels of tumor‐specific CTL and eventually, a reduced tumor growth. Now we aim at analyzing whether α‐MSH controls MDSC expansion and function in samples from human skin tumor patients as well. For this purpose, we will generate MDSC from PBMC of subjects with basal cell and squamous cell carcinomas or MM in the presence or absence of α‐MSH and characterize their phenotype as well as their suppressive activity. To assess the role of MC‐1R signaling in this process we will compare data from patients having a loss‐of‐function mutation in the MC‐1R gene to data from patients with a functional MC‐1R. Taken together, with this project we intend to investigate whether α‐MSH might in the future be suitable for the development towards an adjuvant treatment in skin cancer, which is of interestsince NDP‐MSH, a stabilized synthetic analogue of α‐MSH, has been approved for the treatment of rare inherited metabolic disorders (such as EPP) and thus, could perhaps be repurposed for cancer therapy. After having shown the effect of MSH on MDSCs in skin cancer we intend to expand our knowledge to samples from patients with other tumor entities.