Unleashing natural IL-18 activity using an anti-IL-18BP blocker antibody induces potent immune stimulation and anti-tumor effects (Control # 24-A-4896-AACR)


IL-18 is an inflammasome induced proinflammatory cytokine that augments T and NK cell activity and stimulates IFNγ production. The activity of IL-18 is naturally blocked by a high affinity endogenous binding protein (IL-18BP). IL-18BP is induced in the tumor microenvironment (TME) in response to IFNγ upregulation in a negative feedback mechanism. By evaluating 88 human tumor specimens and serum samples we were able to show that IL-18 is upregulated in the TME (median 11.2ng/gr) compared to serum samples (median 0.3ng/ml). Moreover, we showed that most of the IL-18 is bound by IL-18BP. IL-18BP-bound IL-18 levels were largely above the amount required for T cell activation in vitro (1.2ng/gr), implying that blocking IL-18BP has the potential to release IL-18 in tumors above the minimum range required for immune system stimulation. Next, to assess whether tumor endogenous IL-18 levels released by IL-18BP blockade are sufficient to provoke anti-tumor responses, COM503, a high affinity (<1pM) anti-IL-18BP Ab, was generated and examined in T and NK cell-based assays. In a co-culture assay of tumor cells with ex-vivo stimulated human tumor infiltrating CD8+ lymphocytes, COM503 was able to displace IL-18 from a pre-formed complex and enhance IFNγ (197%, p<0.01) and TNFα (84% p<0.01) secretion. Additionally, COM503 induced human NK cell activation as reflected by increased IFNγ secretion (26-fold, p<0.001). Finally, in human ex vivo dissociated tumor cells assay, COM503 mediated an increase in Granzyme B (25%), IFNγ (38%), TNFα (58%) and IL-12 (50%) production. In vivo, administration of an anti-mouse IL-18BP Ab resulted in potent anti-tumor responses and increased survival across multiple mouse tumor models. In orthotopic E0771 tumor model, anti-IL-18BP Ab induced significant tumor growth inhibition (91% TGI, p<0.0001), as well as pronounced TME-localized immune modulation. This modulation included an increase in CD8+ T cells expansion (108.5%, p=0.015) and activation, specifically in polyfunctional
effector IFNγGrB+CD8+ T cells (259%, p=0.02) and IFNγ+TNFα+NK cells (77%, p=0.001). Similarly, anti-tumor effects were shown in MC38OVA\textsuperscript{dim} model (58% TGI, p<0.001), accompanied by a robust TME-localized immune modulation including increased CD8+ T cells expansion (85%, p=0.009) and IFNγ secretion (76%, p=0.052). In contrast to immune modulation in the TME, no increase in inflammatory cytokines and lymphocyte numbers or activation state was observed in serum and spleen. Taken together, our data suggest that IL-18 is upregulated in the TME, mostly bound by IL-18BP, and could be exploited to induce pronounced TME-localized immune modulation. Anti-IL-18BP Ab approach has a leading edge in inhibiting tumor growth while avoiding peripheral toxicity associated with administration of a cytokine. COM503 is currently undergoing IND-enabling studies.