ABSTRACT

IL-2 has been used in cancer therapy and also for other applications like treatment of chronic viral infections or as an adjuvant for vaccines. However, treatment with IL-2 is rather difficult due to its severe side effects. These toxicities, associated with high-dose treatment necessary for IL-2 to function, have been found the most limiting factor for IL-2 applications. Further, particular anti-IL-2 monoclonal antibodies (mAb) can actually increase biological activity of IL-2 rather than block it. Binding of IL-2 to anti-IL-2 mAb creates a superagonistic immunocomplexes which have dramatically higher and selective biological activity in comparison to free IL-2 *in vivo*. Such approach may finally overcome the difficulties associated with administration of IL-2, thus opening brand new scopes for IL-2 and its application not only in the field of tumor therapy.

We have shown that IL-2 immunocomplexes composed of IL-2 and anti-IL-2 mAb S4B6 (IL-2/S4B6) stimulate predominantly cells expressing CD122 and CD132 (dimeric IL-2 receptor), i.e. NK and MP $CD8^+$ T cells, with T_{reg}, γδ T and NKT cells being expanded as well. IL-2/S4B6 are able to drive the expansion of activated naive $CD8^+$ T cells into functional memory-like $CD8^+$ T cells. Moreover, these immunocomplexes exert therapeutical potential alone or in combination with novel type of cytostatics based on poly(*N*-(hydroxypropyl) metacrylamide) (HPMA) on several experimental tumor models (e.g. BCL1 leukemia and B16F10 melanoma). Prophylactic regimens of IL-2/S4B6 led to survival of one-third (BCL1) or up to two-thirds (B16F10) of tumor bearing mice, depending on the IL-2/S4B6 dosage. Application of HPMA copolymer-bound doxorubicin conjugate followed by repeated IL-2/S4B6 treatment prolongs survival or even completely cures mice with tumors in very late progression stages.

The second kind of immunocomplexes studied, composed of IL-2 and anti-IL-2 mAb JES6.1 (IL-2/JES6.1) and specific for cells expressing CD25, drive expansion of activated $CD8^+$ T and T_{reg} cells. We have shown that such increase of T_{reg} cell numbers accelerate BCL1 leukemia progression *in vivo*. Finally, we have also shown that increased biological activity of IL-2 immunocomplexes is probably governed by considerable prolonged half-life in circulation.

In conclusion, our findings have contributed to better knowledge of IL-2 immunocomplexes and their mechanisms of function, which may also result in quicker translation into wide array of possible applications in human medicine.