# Editorial

# Interleukin 12 in Cancer Treatment

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Interleukin 12 (IL-12) is made up of two disulphide-linked chains, p35 and p40. The cytokine is produced by monocytes, macrophages, myeloid dendritic cells and B cells. It stimulates development of NK cells and TH1 differentiation of $CD4^+$ T cells, thus participating in the regulation of the immune response (for a review, see Klein and Hořejší, 1997; Grufman and Kärre, 2000; Jinushi and Tahara, 2009). Recently, the structurally similar but functionally different cytokine IL-23 displaying anti-tumour effects and related to the IL-12 family of cytokines was discovered (Engel and Neurath, 2010). In a variety of experimental tumour models it has been demonstrated that tumour immunogenicity could be enhanced by administration of IL-12 or by gene therapy employing insertion of the *IL12* gene into tumour cells (for a review, see Bubeník, 1996; Bubeník et al., 2000; Bubeník, 2008). IL-12 is known to activate IFN-γ production by NK and T cells and development of cytotoxic T lymphocytes *in vitro* (Grufman and Kärre, 2000; Dranhoff, 2004; Indrova et al., 2008, 2009). IL-12 was also found to have anti-angiogenic activity, apparently through the induction of IFN-γ-inducible protein 10 (Sgadari et al., 1996). Each of these properties of IL-12 may contribute to the anti-tumour activity (Tsung et al., 1998). However, serious toxicity has been associated with the IL-12 systemic administration. Therefore, peritumoral administration of IL-12, expression of the *IL12* genes in the peritumoral milieu after injection of *IL12* gene-modified vaccines, or nanoparticle-based gene delivery (Hallaj-Nezhadi et al., 2010) were considered to help avoid the systemic toxicity. It has also been shown that the *IL12* gene-modified cellular vaccines augment the efficacy of cancer surgery and chemotherapy in experimental models mimicking some human tumours (Indrová et al., 2006, 2008; Malvicini et al. 2009; Bubeník and Šímová, 2009). With regard to the mechanism of these IL-12 effects, it was reported that IL-12 is an indispensable cytokine for activating dendritic cells (Jinushi and Tahara, 2009). It stimulates dendritic cell-mediated cross-presentation of tumour-associated antigens and promotes the TH1 differentiation crucial for tumour defence mechanisms (Engleman 2003; Dranhoff, 2004). The administration of DNA encoding human IL-12 by intratumoral injection into patients with metastatic melanoma (Heinzerling et al., 2005), intratumoral injection of a recombinant canarypox virus expressing IL-12 (Triozzi et al., 2005), IL-12 plasmid electroporation (Daud et al., 2008), *IL12* gene therapy by peritumoral injection of IL-12-transduced autologous fibroblasts (Kang et al., 2001), vaccination with *IL12* gene-modified autologous melanoma cells (Sun et al., 1998), utilization of IL-12 plasmid/lipopolymer complexes for the treatment of recurrent ovarian cancer (Anwer et al., 2010), treatment of multiple myeloma by subcutaneous IL-12 injections (Lacy et al., 2009), as well as other procedures (for a review see Jinushi and Tahara, 2009) were found to induce local immune responses, to enhance cellular and humoral immune reactions, as well as to prolong survival of patients and to decrease tumour neoangiogenesis.

Taken together, preclinical studies as well as phase I–III clinical trials have clearly demonstrated that local IL-12 therapy and peritumoral administration of the IL-12-based tumour vaccines can induce and enhance tumour immunity and by this way prolong survival of the tumour-bearing individuals. In addition, utilization of the IL-12-based therapeutic procedures as adjuvant treatment together with conventional therapeutic modalities, chemotherapy and surgery also provided promising results. However, many technical problems have still to be solved (Berrando et al., 2009) and the translational therapeutic trials have to be carefully evaluated before the definitive conclusions regarding the actual therapeutic potency of this novel and promising strategies for the management of cancer patients can be drawn and relevant therapeutic protocols can be designed.

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