“Designer cytokines” targeting the tumor vasculature—think global and act local

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Tumor necrosis factor (TNF) was discovered in 1975 as a lipopolysaccharide-induced serum factor that causes necrosis of tumors (Carswell et al., 1975). It was later found that TNF and cachectin, a factor causing wasting disease, were one and the same molecule (Beutler et al., 1985). Studies on the inflammatory activity of TNF have been translated into clinical success, namely blocking antibodies used to suppress autoimmune diseases. Research on TNF anti-tumor activity, in contrast, has not yet resulted in a therapeutic breakthrough. This may change, based on a study by Huyghe et al (2020) describing novel “designer cytokines” (TNF and interferon-γ) that increase local activity by targeting the CD13-positive tumor vasculature, while simultaneously lowering the binding affinity to the respective cytokine receptor, thereby reducing off-target effects on normal cells.

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See also: L Huyghe et al

In their study, Huyghe et al (2020) have combined both strategies and thus improved efficacy and safety for the therapeutic use of TNF and IFNγ (Huyghe et al., 2020). First, they succeeded in increasing the local cytokine concentration at the tumor site by attaching a CD13-specific single-chain antibody to the cytokines. Second, they mutated TNF (by changing amino acid 87 Y to F) and IFNγ (by truncating 8 C-terminal amino acids), thereby reducing the biological activity approx. 10,000- and 7,000-fold, respectively. This resulted in decreased systemic toxicity (Fig 1C). The novel TNF could also improve adoptive T-cell therapy using engineered with chimeric antigen receptors by increasing the number of T cells infiltrating the tumor. In mice with endothelial-specific TNFR1 expression, tumors could be eradicated without measurable toxicity. However, tumor-activated vessels are not the only ones highly susceptible to the destructive TNF effects, also vessels exposed to bacterial products react strongly to TNF with systemic or local Schwartzman reactions (Rothstein & Schreiber, 1988). It would therefore be important to test whether endothelial cells that are activated during bacterial infections could become CD13-positive targets of the novel designer cytokines. Finally, it should be mentioned that there is a third powerful strategy to locally release therapeutic amounts of TNF and IFNγ, which is the transfer of tumor antigen-specific T cells that release the cytokines upon antigen encounter.

Clinical studies that specifically direct cytokines such as TNF or IFNγ to the tumor endothelium via peptides or single-chain antibodies are already underway. Huyghe et al’s elegant approach, however, makes it possible to concentrate the effect of the cytokines more precisely to the tumor site, thereby increasing the therapeutic effect and avoiding negative side effects and systemic toxicity. Therefore, this work is certainly an important step forward for the development of “designer cytokines” that are suitable for clinical application.

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