“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 against the cytokine receptor, thereby reducing off-target effects on normal cells.

Two different strategies have been developed to reduce systemic toxicity of TNF or IFNγ while preserving their anti-tumor activity. The first one consists in specifically targeting the cytokines to CD13, a marker predominately expressed on tumor vasculature. Targeting was achieved using either peptides or single-chain antibodies directed against CD13 (Fig 1B). Pre-clinical data suggest that such approaches are feasible and may improve local therapeutic anti-tumor activity (Johansson et al., 2012; Corti et al., 2013). The second strategy to reduce unwanted side effects is based on changing the molecular interactions between TNF or IFNγ and their receptors. A prime example of such a strategy is the study by Mendoza et al. (2019) in which, based on the crystal structure of the IFNγ signaling complex, specific signaling agonists were designed by changing contact residues between the ligand and receptor chains, resulting in a molecule with reduced side effects for immunotherapy.

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 T cells 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 re-act 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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Figure 1. Strategies to use TNF as an anti-cancer agent.

(A) Using recombinant tumor necrosis factor (TNF) that binds to the TNF receptor (TNFR) on all cells in the body causes toxicity and prohibits clinical application. (B) Fusing TNF to a single-chain antibody targeting CD13 that is preferentially expressed on tumor vasculature concentrates its activity to the tumor site but does not exclude off-target effects as it still binds to TNFR on all other cells in the body. (C) The novel "designer cytokine" approach developed by Hyghe et al combines selective targeting of TNF to the tumor vasculature using a CD13-specific single-chain antibody and mutating the TNF molecule (Y87F) to decrease the binding to TNFR and avoid systemic toxicity.

References
Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YC, Mathison J, Ulevitch R, Cerami A (1985) Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature 316: 552 – 554
Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B (1975) An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA 72: 3666 – 3670
Corti A, Curnis F, Rossoni G, Marcucci F, Gregorc V (2013) Peptide-mediated targeting of cytokines to tumor vasculature: the NGR-hTNF example. BioDrugs 27: 591 – 603
ten Hagen TL, Seynhaeve AL, Eggermont AM (2008) Tumor necrosis factor-mediated interactions between inflammatory response and tumor vascular bed. Immunol Rev 222: 299 – 315
Huyghe L, Van Parys A, Cauwels A, Van Lint S, Hostens J, Goethals A, Vanderroost N et al (2020) Safe eradication of large established tumors using neovascular-targeted tumor necrosis factor-based therapies. EMBO Mol Med 12: e12223
Johansson A, Hamzah J, Payne CJ, Ganss R (2012) Tumor-targeted TNFalpha stabilizes tumor vessels and enhances active immunotherapy. Proc Natl Acad Sci USA 109: 7841 – 7846
Kammertoens T, Friese C, Arina A, Idel C, Briesemeister D, Rotte M, Ivanov A, Szymborska A, Patone G, Kunz S et al (2017) Tumour ischaemia by interferon-gamma resembles physiological blood vessel regression. Nature 545: 98 – 102
Mendoza JL, Escalante NK, Jude KM, Sotolongo Bellon J, Su L, Horton TM, Tsutsumi N, Berardinelli SJ, Haltiwanger RS, Piehler J et al (2019) Structure of the IFNgamma receptor complex guides design of biased agonists. Nature 567: 56 – 60
Rothstein JL, Schreiber H (1988) Synergy between tumor necrosis factor and bacterial products causes hemorrhagic necrosis and lethal shock in normal mice. Proc Natl Acad Sci USA 85: 607 – 611

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