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Immunity boost and increased lifespan of tumor necrosis factor-α/CD40 ligand-engineered mesenchymal stem cells administred in mice

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The interaction between mesenchymal stem cells (MSCs) and dendritic cells (DCs) affects T cell development and function. Further, the chemotactic capacity of MSCs, their interaction with the tumor microenvironment and the intervention of immune-stimulatory molecules suggest possible exploitation of tumor necrosis factor-α (TNF-α) and CD40 ligand (CD40L) to genetically modify MSCs for enhanced cancer therapy. Both DCs and MSCs were isolated from BALB/c mice. DCs were then cocultured with MSCs transduced with TNF-α and/or CD40L [(TNF-α/CD40L)-MSCs]. Major DCs' maturation markers, DC and T cell cytokines such as interleukin-4, -6, -10, -12, TNF-α, tumor growth factor-β, as well as T cell proliferation, were assessed. Meantime, a BALB/c mouse breast tumor model was inducted by injecting 4T1 cells subcutaneously. Mice (n = 10) in each well-defined test groups (n = 13) were cotreated with DCs and/or (TNF-α/CD40L)-MSCs. The controls included untreated, empty vector-MSC, DC-lipopolysaccharide and immature DC mouse groups. Eventually, cytokine levels from murine splenocytes, as well as tumor volume and survival of mice, were assessed. Compared with the corresponding controls, both *in vitro* and *in vivo* analyses showed induction of T helper 1 (Th1) as well as suppression of Th2 and Treg responses in test groups, which led to a valuable antitumor immune response. Further, the longest mouse survival was observed in mouse groups that were administered with DCs plus (TNF-α/CD40L)-MSCs. In our experimental setting, the present pioneered study demonstrates that concomitant genetic modification of MSCs with TNF-α and CD40L optimized the antitumor immunity response in the presence of DCs, meantime increasing the mouse lifespan.

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