eTable 4. Senescence and immunomodulatory markers analyzed by flow cytometry

Marker	Biological relevance	Relevance in diseases	Ref.
CD28	- Costimulatory molecule - Downregulation due to repeated antigen exposure is a hallmark of cellular senescence - CD28- T cells display cytotoxic capacities, resistance to apoptosis	- Expansion of CD28- T cells in peripheral blood during natural aging, virus infection (e.g. HIV, CMV), autoimmune diseases (e.g. RA, SLE, MS) - CD4+CD28- T cells found in brain lesions of MS patients, exhibited pathogenic properties contributing to tissue damage	e6–11
CD57	- Marker for replicative senescence - Expressed on highly differentiated T cells	- Expansion in individuals with chronic immune activation (e.g. HIV) and during natural aging	e11–13
KLRG1	- Coinhibitory molecule - Highly expressed on human differentiated memory T cells - Marker for replicative senescence	- Increased frequencies during natural aging and virus infection (e.g. CMV, EBV, HIV)	e13–15
LAG3	- Coinhibitory molecule - Exhaustion marker - Inhibits inflammatory responses	- Increased expression during virus infection (e.g. HIV) - Deficiencies in the LAG-3 pathway linked to the development of autoimmune diseases (autoimmune diabetes, RA)	e16–20
CTLA-4	- Coinhibitory molecule - Exhaustion marker - Inhibits inflammatory responses	- Increased expression during virus infection (e.g. HIV) - CTLA-4 deficiency in animal models is linked to development of autoimmune disorders (e.g. SLE) - Further human clinical studies are necessary to proof the efficacy CTLA-4 blockade in patients with autoimmune disorders	e16,17,21
CD226 (DNAM-1)	- Costimulatory molecule - Modulates inflammatory signaling pathways contributing to CNS autoimmunity, proliferation, adhesion, differentiation of T cells	- CD226 promotes proinflammatory Th1 and Th17 responses driving pathogenesis of autoimmune disorders (e.g. MS) - Genetic variants in CD226 lead to a higher susceptibility to develop MS - CD226 deficiency in animal models for MS and typ 1 diabetes leads to an amelioration of symptoms	e22–28

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus