Normal and Neoplastic Stem Cells

Irv Weissman
 Stem Cell Institute, Stanford University, Stanford, CA, United States

Tissue stem cells regenerate the body and are the only cells that maintain self-renewal throughout life. When stem cells divide they give rise to stem cells (by self-renewal) and progenitors (by differentiation). Stem cell isolation and transplantation is the basis for regenerative medicine. We isolated mouse and then human hematopoietic stem cells (HSCs). Importantly, the transplantation of purified HSCs results in complete regeneration of the blood and immune systems without causing graft vs, host disease, and can induce permanent transplant tolerance of any organ or cell from the HSC donor. In a clinical trial in metastatic breast cancer patients treated with myeloablative chemotherapy combinations, HSC purification made autologous transplantation to cancer patients possible, without including cancer cells in the graft. The 15-year overall survival rate was ~7% in recipients of mobilized peripheral blood (MPB) autologous transplantation, and ~33% in recipients of cancer-free HSCs.

Preleukemic progression: To study the relationship between stem cells and cancer, we followed the progression from hematopoietic stem cells (HSCs) to myelogenous leukemias and found that the developing pre-cancerous clones progress and accumulate mutations at the stage of HSCs, with the last mutation giving rise to leukemia stem cells (LSC). At this point, the leukemia stem cell is a downstream oligolineage or multilineage progenitor that has evaded programmed cell death and programmed cell removal, and also acquired self-renewal.

A checkpoint inhibitor for innate immunity macrophages: By comparing leukemia stem cells to HSC, we identified CD47 overexpression on LSC, and then on all cancers tested, and showed that it is a cell surface molecule used by live cancer cells to evade macrophage phagocytosis by binding to its receptor, SIRPa on macrophages. CD47 is perhaps the first target that is expressed on all human cancers tested. In pre-clinical research using patient derived xenografts anti-CD47 antibodies or blocking agents that neutralize the inhibitory effect of CD47-SIRPa interaction enabled macrophages to engulf and eliminate cancer cells. Importantly, antibody blockade of CD47 did not affect most normal cells, expressing CD47, because cancer cells, but not normal cells, express an 'eat me' signal, calreticulin; thus blockade of the 'don't eat me' signal CD47 leads to selective removal of cancer and not normal cells. Calreticulin is mainly produced and secreted by activated macrophages, and binds to cancer cell surface asialoglycans; the bound calreticulin binds also to CD91, the macrophage prophagocytic receptor.Other IgG1 anti-cancer antibodies rituximab, trastuzimab, cetuximab, and anti-PDL1 provide strong prophagocytic signals via macrophage Fc

receptors, and anti-CD47 is synergistic with them. The CD47/calreticulin axis also operates in models of atherosclerosis and fibrosis. Humanized clinical grade IgG4 anti-CD47antibodies are in phase 1/2 clinical trials. One such trial, published in the New England J Medicine (Advani et. el), demonstrated that the anti-CD47 combination with Rituximab led to responses in patients with highly aggressive DLBCL and FL who were relapsed and refractory to Rituxan and chemotherapy; The combined response rate was nearly 50%, with 70-80% of these in complete remission to date. Additional 'don't eqt me' receptor-ligand pairs include macrophage LILRB1:cancer cell MHC I beta2M, and macrophage PD1:cancer cell, PDL1.