Enhancing immune-mediated killing of senescent cells

S-01.2-1

J. Gil[I]

[I]Imperial College London, London, United Kingdom

Senescent cells are induced in response to oncogenic activation and tissue damage and are normally cleared by the immune system. When the immune surveillance of senescent cells is not effective, senescent cells linger, as happens in aged, cancerous and fibrotic tissues. This aberrant accumulation of senescent cells is associated with cancer and multiple age-related diseases. Recently, drugs that selectively kill senescent cells, termed senolytics, have proven beneficial in improving the outcomes of many of these pathologies. An alternative way to clear senescent cells is by potentiating their immune-mediated clearance. I will describe our screens to identify ways to enhance the elimination of senescent cells by Natural Killer (NK) cells. We identify that SMARCA4 regulates the secretion of immunomodulatory chemokines by senescent cells. A PROTAC targeting SMARCA4 increases the senescence-associated secretory phenotype (SASP), enhances NK-mediated killing of senescent cells and synergises with cisplatin to increase the infiltration of CD8 T cells and mature, activated NK cells in an immunocompetent model of ovarian cancer. Our results indicate that SMARCA4 inhibitors enhance NK-mediated surveillance of senescent cells and may represent senotherapeutic interventions for ovarian cancer and other senescence-associated diseases.