Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging

Marjolein P. Baar1, Renata M.C. Brandt1, Diana A. Putavet1, Julian D.D. Klein1, Kasper W.J. Derks1, Benjamin R.M. Bourgeois7, Sarah Stryeck7, Yvonne Rijksen7, Hester van Willigenburg1, Danny A. Feijtel1, Ingrid van der Pluijm1,4, Jeroen Essers1,4,5, Wiggert A. van Cappellen5, Wilfred F. van IJcken2, Adriaan B. Houtsmuller2, Joris Pothof3, Ron W.F. de Bruin6, Tobias Madl7, Jan H.J. Hoeijmakers1, Judith Campisi8,9, Peter L.J. de Keizer1,8,10.

Abstract

The accumulation of irreparable cellular damage restricts healthspan after acute stress or natural aging. Senescent cells are thought to impair tissue function, and their genetic clearance can delay features of aging. Identifying how senescent cells avoid apoptosis allows for the prospective design of anti-senescence compounds to address whether homeostasis can also be restored. Here, we identify FOXO4 as a pivot in senescent cell viability. We designed a FOXO4 peptide that perturbs the FOXO4 interaction with p53. In senescent cells, this selectively causes p53 nuclear exclusion and cell-intrinsic apoptosis. Under conditions where it was well tolerated in vivo, this FOXO4 peptide neutralized doxorubicin-induced chemotoxicity. Moreover, it restored fitness, fur density, and renal function in both fast aging XpdTTD/TTD and naturally aged mice. Thus, therapeutic targeting of senescent cells is feasible under conditions where loss of health has already occurred, and in doing so tissue homeostasis can effectively be restored.

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Michael Boivin-Welch
(Laboratoire Dr Manuel Caruso)

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