EBioMedicine 74 (2021) 103693

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Development of a novel senolytic by precise disruption of FOXO4-p53 complex

Utkarsh Tripathi[a], Selim Chaib[a], Erin O. Wissler Gerdes[a], Kelly A. Hogan[a,c], Yi Zhu[a,b,*]

[a] Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN, USA
[b] Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA
[c] Laboratory of Metabolism and Molecular Nutrition, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Article History:
Received 28 October 2021
Accepted 28 October 2021
Available online xxx

The first senolytic agents, senescent cell-eliminating drugs Dasatinib, Quercetin, Fisetin, and Navitoclax were discovered through a hypothesis-driven approach [2–5]: Senescent cells remain viable by inactivating senescence cell anti-apoptotic pathways (SCAPs) including ephrins, PI3K isoforms, p53/p21^{CIP1}, HIF-1α, plasminogen activated inhibitors 1 and 2, and Bcl-2 family members [2]. Therefore, the first senolytics were developed to target SCAP signalling.

The work of Le et al. in *EBioMedicine* [6] is based on the previously reported involvement of the FOXO4-p53 complex [1], a key regulator of SCAPs. FOXO4 is elevated in senescent cells and essential for maintaining viability of senescent cells by sequestering p53 in the nucleus [1]. Baar *et al.* [1] developed a peptide named FOXO4-DRI to disrupt the FOXO4-p53 interaction by binding to p53 and inducing p53/p21^{CIP1}-dependent apoptosis in senescent cells (Fig. 1). In this study, Le et al. [6] take a different approach by disrupting the FOXO4-p53 interaction with FOXO4 blocking peptides, which enable release and activation of p53. Using an atomistic model to simulate the FOXO4-p53 interaction, Le et al. identify the CR3 domain on FOXO4. A series of peptides were then designed to target high-affinity binding to the CR3 domain. Le et al. [6] further test these putative senolytic peptides in a wide range of senescent cell types. ES2 peptides show the most potent senolytic activity among others and are 3-7 times more effective than the previously reported peptide FOXO4-DRI in both in-vitro and in-vivo studies. Le et al. [6] highlight the safety and efficacy of ES2 in combination with the chemotherapeutic Dabrafenib as a one-two punch therapy in preclinical mouse models of melanoma.

Chemotherapeutics can induce senescence in both cancer and noncancer cells, which promote cancer recurrence and accelerated aging phenotypes [7]. Eliminating therapy-induced senescent cells (TIS) might be an effective strategy to prevent tumour relapse and reduce the long-lasting effects of the disease [8]. Given the heterogeneity of senescent cancer cells in tumour regions and TIS in normal tissues at sites distal to a tumour, the selection and design of senolytics as therapeutics warrant extensive evaluation. Le et al. [6] show compelling evidence for efficacy of senolytics in multiple xenograft cancer models. Notably, the combined therapies of ES2 and a Braf inhibitor result in greater elimination of both cancer and senescent cells as well as significant improvement in survival compared to chemotherapy alone. One caveat to the observations of Le et al. is that senescent cancer cells may not achieve a state of permanent growth arrest and may acquire stemness through mutations leading to drug resistance and ultimately metastasis [9]. Thus, interrogating the long-term effects of senolytics in cancer relapse in treated mice would provide more insight into the true translational potential of this senolytic peptide.

It is worth noting that senescent cells are heterogeneous and vary in SCAPs among tissues of different cell lineages. Therefore, questions to be resolved include understanding which types of senescent cells are responsible for cancer relapse and post-chemotherapy sequelae; and which types of senescent cells are targeted by senolytics. Taken together, use of this class of senolytics clinically requires a deeper understanding of the molecular and functional signatures of eliminated senescent cells as well as characterization of the impact of these drugs on healthy cells. Characterizing senescent cells is necessary to target disease-associated senescent cells while sparing immune-modulating senescent cells or senescent cells required for repair and wound healing [10]. More rigorous elucidation of the mechanisms of action and toxicity of senolytics, specifically their anti-apoptotic properties, is necessary to cultivate the next generation of senescent cell eliminating drugs.

Contributors

YZ, UT, and SC wrote the original draft. YZ, EW, and KH revised and edited the final draft.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103646.
* Corresponding author at: (1)200 First St., S.W., Rochester, MN 55905, USA
E-mail address: Zhu.Yi@Mayo.edu (Y. Zhu).

https://doi.org/10.1016/j.ebiom.2021.103693

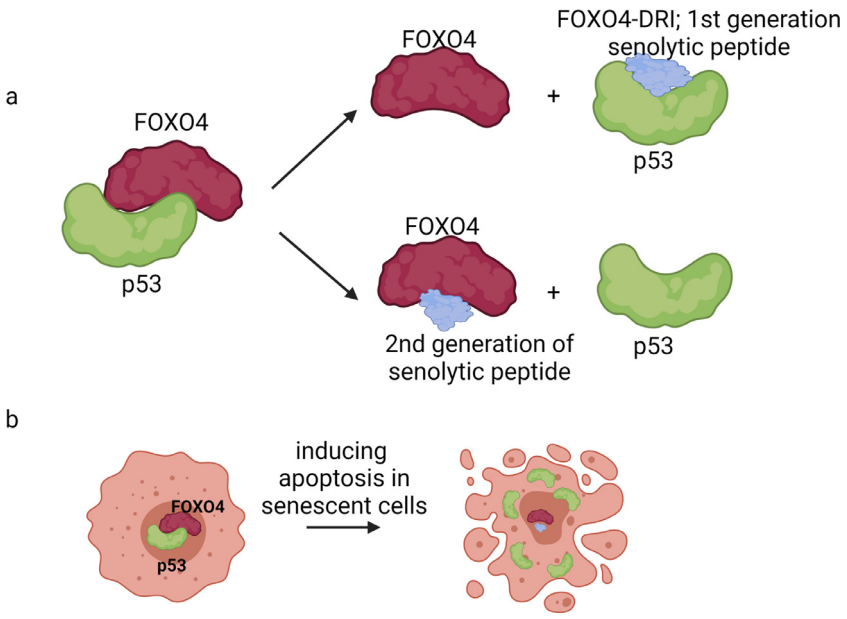

Fig. 1. Illustration of senolytic peptide design. a) Two alternative approaches for designing a senolytic peptide to disrupt FOXO4-p53 interaction. b) Disruption of the FOXO4-p53 complex releases active p53 and induces apoptosis in senescent cells.

References

[1] Baar MP, Brandt RMC, Putavet DA, Klein JDD, Derks KWJ, Bourgeois BRM, et al. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell 2017;169(1) 132-47 e16.

[2] Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell 2015;14(4):644–58.

[3] Zhu Y, Tchkonia T, Fuhrmann-Stroissnigg H, Dai HM, Ling YY, Stout MB, et al. Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. Aging Cell 2016;15(3):428–35.

[4] Zhu Y, Doornebal EJ, Pirtskhalava T, Giorgadze N, Wentworth M, Fuhrmann-Stroissnigg H, et al. New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463. Aging (Albany NY) 2017;9(3):955–63.

[5] Yousefzadeh MJ, Zhu Y, McGowan SJ, Angelini L, Fuhrmann-Stroissnigg H, Xu M, et al. Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine 2018;36:18–28.

[6] Le HH, Cinaroglu SS, Manalo EC, Ors A, Gomes MM, Duan Sahbaz B, et al. Molecular modelling of the FOXO4-TP53 interaction to design senolytic peptides for the elimination of senescent cancer cells. EBioMedicine 2021 Oct 21;73:103646. doi: 10.1016/j.ebiom.2021.103646.

[7] Wyld L, Bellantuono I, Tchkonia T, Morgan J, Turner O, Foss F, et al. Senescence and Cancer: A Review of Clinical Implications of Senescence and Senotherapies. Cancers (Basel) 2020;12(8).

[8] Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biology 2008;6(12):2853–68.

[9] Milanovic M, Fan DNY, Belenki D, Däbritz JHM, Zhao Z, Yu Y, et al. Senescence-associated reprogramming promotes cancer stemness. Nature 2018;553(7686):96–100.

[10] Tripathi U, Misra A, Tchkonia T, Kirkland JL. Impact of senescent cell subtypes on tissue dysfunction and repair: importance and research questions. Mech Ageing Dev 2021;198:111548.