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Senescent Surfaceome Targeting: Developments in DPP4-Antibody Functionalized Nanoparticles for Senolytic Cancer Treatment

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ABSTRACT: The progression of cancer and its treatment are both impacted by cellular senescence. Senescent cells can stop tumor growth, but their lingering presence encourages inflammation and recurrence. The development of mesoporous silica nanoparticles (MSNs) functionalized with DPP4-targeting antibodies for selective senolysis is highlighted in this review. We explore how targeting the senescent surfaceome represents a promising frontier in precision nanomedicine by assessing existing approaches and recent discoveries, especially the investigation of DPP4-targeted nanoparticles loaded with navitoclax.

INTRODUCTION

Senescence, which is characterized by irreversible cell cycle arrest, is a feature of both aging and stress brought on by therapy. Senescent cells, which have a unique secretome (SASP), changed membrane proteins, and increased β-galactosidase activity, can paradoxically encourage the growth of tumors if they are not removed after treatment.

Senolytics like Navitoclax provide a way to get rid of these cells. However, because of off-target toxicity, their lack of specificity has hindered clinical translation. These drawbacks could soon be addressed by novel strategies that make use of delivery systems based on nanoparticles.

CANCER SENESCENCE: DIFFICULTIES WITH TARGETED TREATMENT

Senescence-inducing treatments for a variety of cancers are approved, including palbociclib and CDK4/6 inhibitors. However, relapse is frequently caused by the persistence of senescent tumor cells. Because they are expressed in non-senescent cells like macrophages, markers like SA-β-gal, which are the basis of traditional senolytic strategies, lack specificity (1-10).

Important Restrictions:

• Current senolytics have off-target effects; • There is no universal senescence biomarker; • β-gal activity is not limited to senescent cells;

DPP4 AS A THERAPEUTIC TARGET AND THE SENESCENT SURFACEOME

According to recent research, DPP4 (CD26), a member of the senescent surfaceome, is a promising biomarker. Surface proteins allow extracellular targeting, which improves selectivity and lowers systemic exposure in contrast to intracellular markers.

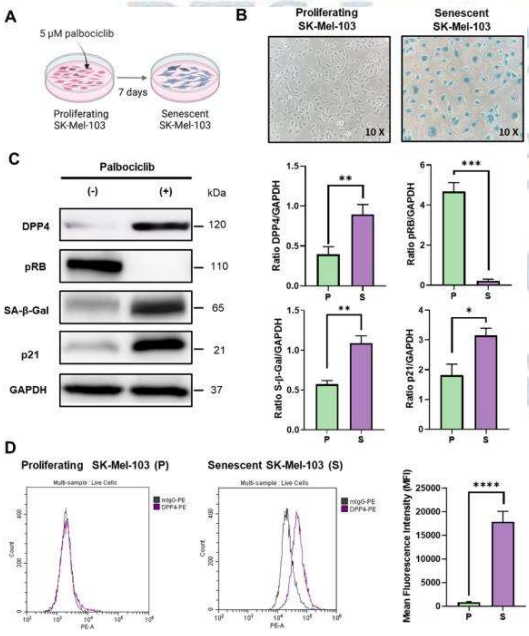

Figure 1. Senescent melanoma cells with overexpressed DPP4

DEVELOPING NANOPARTICLES TARGETED BY DPP4

Mesoporous silica nanoparticles (MSNs) have the following benefits:

High drug-loading capacity, biocompatibility, and adjustable surface chemistry. In the cited study, navitoclax-loaded MSNs were conjugated with anti-DPP4 antibodies and functionalized with redox-sensitive PEG that contained disulfide.

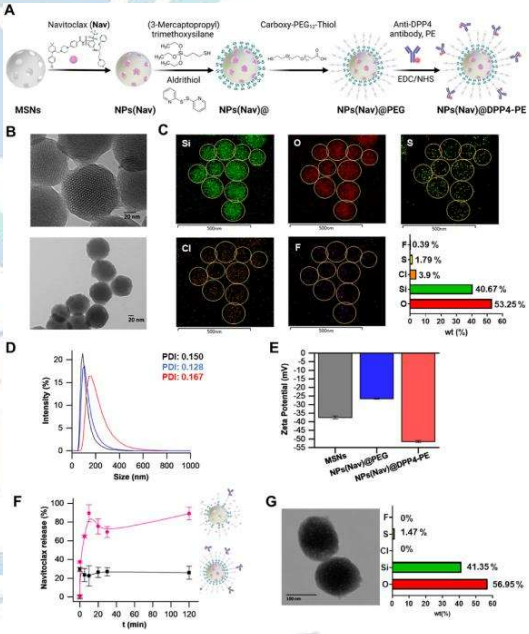

Figure 2. Synthesis and characterization schematic for NPs(Nav)@DPP4-PEAdd important details about the drug release profile, morphology (TEM), and nanoparticle design in Figure 2

VALIDATION IN VITRO AND IN VIVO

It was demonstrated that the created nanoparticles could:

Bind senescent melanoma cells specifically; deliver navitoclax intracellularly upon GSH-mediated cleavage; and selectively trigger apoptosis in senescent cells (11-20).

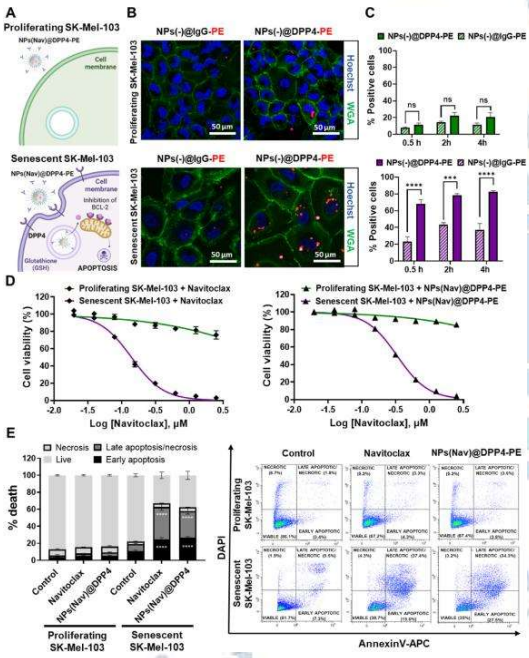

Figure 3. In vitro selective senolysis and nanoparticle uptake

Comparing palbociclib with targeted nanoparticles to free navitoclax or non-targeted controls, in vivo results in xenograft mouse models demonstrated a significant reduction in tumor size (21-30).

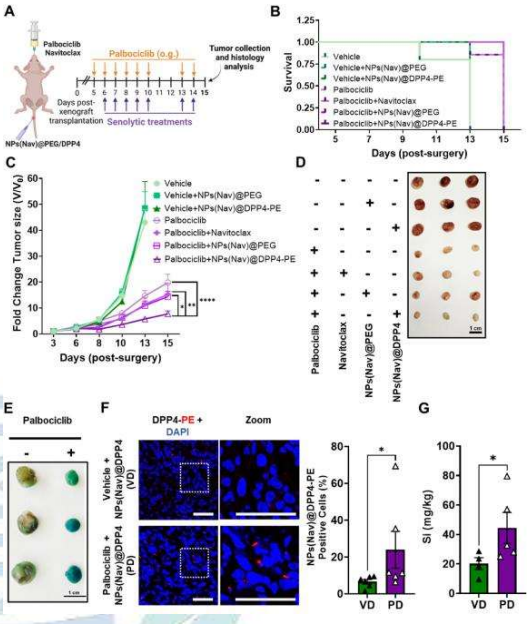

Figure 4. DPP4-targeted therapy causes tumor regression in xenograft models

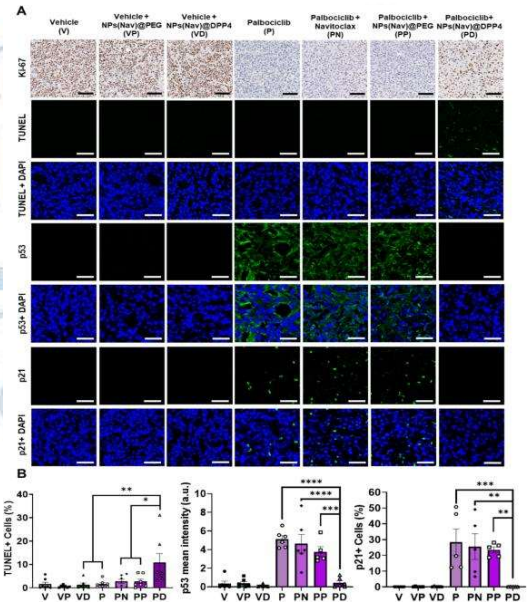

Figure 5. Post-treatment histological analysis (Ki-67, TUNEL, p53, p21)

DISCUSSION

Using DPP4-functionalized NPs in particular to target the senescent surfaceome provides:Increased specificity, regulated intracellular drug release, decreased systemic toxicity, and potential expansion to other aging and chronic inflammatory diseases are all benefits of this approach. It also works in concert with immune-mediated clearance (31-40).

CONCLUSION

Personalized senescence therapy has advanced significantly with the switch from generic senolytics to surfaceome-targeted nanocarriers. The following areas require more research: Long-term safety and biodistribution; Diversity of surfaceomes in other cancer types; Interaction with immunotherapies;

Multifunctional and responsive nanocarriers such as NPs(Nav)@DPP4-PE have potential for clinical translation as our understanding of senescence heterogeneity grows.

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