Inhibition of platelet production

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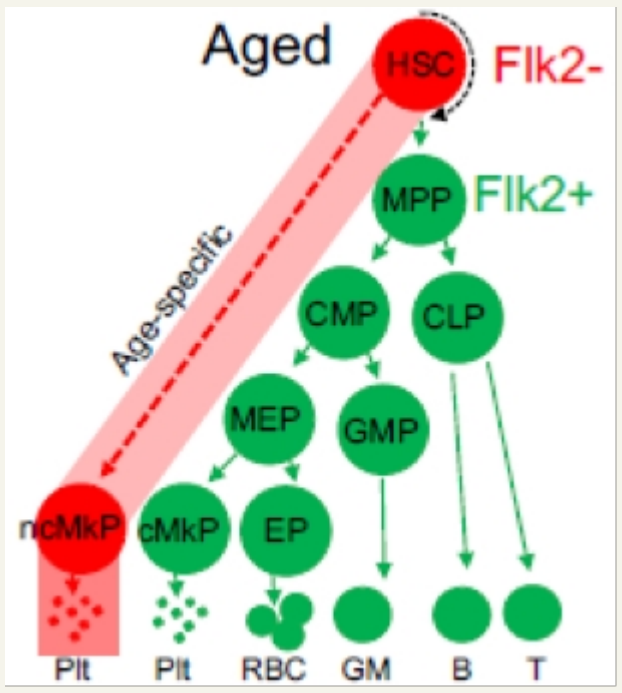
BACKGROUND

The aim of this work is to target the production of age-specific production of hyperactive platelets as a therapeutic platform to control clot formation that causes thrombosis, stroke, heart attacks, and other cardiovascular disease, as well as platelet overproduction disorders such as essential thrombocytosis. In particular, this effort specifically targets cells that have progressed down an age-specific differentiation pathway. These age specific platelets are hyperactive relative to platelets from younger progenitor cells. These older platelet progenitor cells have been characterized molecularly and functionally characterization and can be targeted using pharmacological, antibody-based, cell based or gene therapy based strategies to control clot formation and platelet activity and numbers.

TECHNOLOGY DESCRIPTION

We have identified the cellular culprits that produce age-specific hyperactive platelets (Plts) from hematopoietic stem cells (HSCs) and cause increased risk for cardiovascular disease (CVD). By aging Cre/lox-mediated "FlkSwitch" lineage tracing mice, we uncovered a non-canonical (nc), platelet-specific, direct differentiation path that operates in parallel with the canonical, multiple-intermediate progenitor platelet differentiation pathway (Figure 1).



Strikingly, non-canonical platelets (ncPlts) display higher reactivity and clot formation compared to co-existing canonical platelets (cPlts). The additive pool of hyperactive ncPlts during aging reveal this alternative pathway as the prime suspect in Plt overproduction and hyperactivity that dramatically increase

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OTHER INFORMATION

KEYWORDS

Aging, Platelets, Stem Cells, Hematopoietic Stem Cells, Megakaryocyte Precursor Cells, Cardiovascular Disease, Antibody, Druggable, Gene Therapy, Autologous Gene Therapy

CATEGORIZED AS

- **Medical**
  - Disease: Cardiovascular and Circulatory System
  - Gene Therapy
  - Stem Cell
  - Therapeutics

RELATED CASES

2026-862-0

the risk for CVD in the elderly. CVDs are the leading cause of death and morbidity in aging populations, leading to chronic anti-clotting drug use in millions of patients. Current anti-thrombotic drugs typically target Plt clotting capability directly, without selectivity for the underlying thrombosis risk factors and with variable efficacy. This discovery of an aging-specific HSC differentiation pathway that generates hyperactive Plts opens a novel opportunity to tackle Plt overproduction and hyperactivity at its source: **targeting of age-specific progenitor cells and their aging-selective molecular regulators as an entirely novel strategy for CVD treatments.**

Surface receptor heterogeneity can be leveraged to selectively deplete old HSCs subpopulations by injection of monoclonal antibodies. Preliminary data show robust and durable HSC depletion, with selective reduction of platelets in the peripheral blood.

In addition, these older hematopoietic stem cells can be targeted pharmacologically. The group has identified Nuclear Protein 1 (Nupr1) as a potent molecular regulator of HSC's to non-canonical megakaryocyte precursors (ncMkP's). Other druggable targets of older HSC's have also been identified and tested.

Finally, older HSC's can be targeted through ex vivo gene therapy - HSC's can be isolated from an individual, Nupr1 or other regulators can be altered via CRISPR or other methods and the HSC's with a more "youthful" phenotype reintroduced to the patient.

APPLICATIONS

Antibody based targeting of "elderly" hematopoietic stem cells.

Pharmacological treatment of elderly hematopoietic stem cells to restore them to a more "youthful" phenotype

Autologous gene therapy of elderly hematopoietic stem cells to restore them to a more youthful phenotype

Preventative treatment of cardiovascular disease

Potential extension of lifespan

ADVANTAGES

RELATED MATERIALS

- An age-progressive platelet differentiation path from hematopoietic stem cells causes exacerbated thrombosis - 06/06/2024

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