The serine/threonine kinase PIM3 acts as essential gatekeeper of T cell functions

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Type selection

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General data

Track: Adaptive Immunity

Topic: T cell activation

Abstract text

Text: **Introduction and objective**

Intracellular signaling factors integrating T cell receptor signals are critical targets for immunosuppressive drugs. Drug toxicity and resistance highlight the need for optimization and new molecular targets. This study aims to define and validate PIM3 kinase as a potential therapeutic target for immunosuppressive therapies.

Methods

Expression of PIM kinases was measured in anti-CD3/anti-CD28 activated T cells by qPCR and bulk RNA-Seq. For functional testing we performed CRISPR/Cas9-mediated knockout of PIM3 or retroviral overexpression in primary human $CD4^+$ T cells. Influence of PIM3 inhibitor M-110 on T cell effector functions, such as proliferation, migration and cytotoxicity, was analyzed by flow cytometry. Substrate identification was performed using phospho-proteomics. Human immune organoids were used to investigate modulation of T cell functionality by PIM3 inhibition. Expression of PIM3 by infiltrating T cells in human patient samples was evaluated by scRNA-Seq and immunofluorescence.

Results

We report a selective induction of the serine/threonine kinase PIM3, but not PIM1 and PIM2, in activated human T cells. Specific pharmacological inhibition and CRISPR/Cas9-mediated knockout in primary human T cells uncovered essential roles of this kinase in regulating T cell proliferation, migration, metabolic activity, and cytotoxicity. Furthermore, inhibition of PIM3 resulted in immunosuppressive effects in a human immune organoid allo-rejection model. Mass spectrometry-based target protein identification revealed that PIM3 targets the Ki-67 interacting protein NIFK to control T cell proliferation, establishing a novel regulatory circuit that could be targeted therapeutically in conditions with T cell hyperproliferation. Elevated PIM3 expression was observed in pathological T cell infiltrates in GvHD, psoriasis, and Crohn's disease patients, as well as in pre-clinical psoriasis and colitis models indicating high clinical relevance.

Conclusion

The vital role of PIM3 in T cell function and its elevated expression in hyperproliferative T cell conditions make it a promising target for developing new immunosuppressive therapies.

Conflict of Interest statement

Do you have any conflict of interest to declare?: No

Affirmation

1. Consent to participate and present onsite: Yes

2. Consent to publication publication: Yes

3. Consent on treatment of contact details saved in this system: Yes