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► **To cite this version:**

Francesca Castoldi, Guido Kroemer, Federico Pietrocola. Spermidine rejuvenates T lymphocytes and restores anticancer immunosurveillance in aged mice. *OncoImmunology*, 2022, 11 (1), pp.2146855. 10.1080/2162402X.2022.2146855 . hal-04596717

HAL Id: hal-04596717

<https://hal.science/hal-04596717>

Submitted on 31 May 2024

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Spermidine rejuvenates T lymphocytes and restores anticancer immunosurveillance in aged mice

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ABSTRACT

Writing in *Science*, Al Habsi *et al.* show that spermidine boosts the efficacy of monoclonal antibodies targeting PD-L1 in aged tumor-bearing mice by enhancing fatty acid oxidation in CD8 T cells. These results open new therapeutic avenues to improve the effectiveness of anticancer immunotherapies in aged patients.

ARTICLE HISTORY

Received 4 November 2022
Revised 7 November 2022
Accepted 8 November 2022

KEYWORDS

Aging; autophagy; immune checkpoints; mitochondria

The occurrence of life-threatening illnesses – including cancer – is typically accentuated during the late stages of human lifespan. The age-associated derailment of immune functions (e.g., chronic inflammation and skewing of the antigen repertoires of T cells) may have a pathogenic role in the development of a variety of age-related diseases.¹ Accordingly, interventions that aim at restoring youthful functions of leukocytes are currently being evaluated for their anti-aging effects in preclinical animal models. In the context of malignant transformation, a decline in the fitness of aged CD8 T cells synergizes with malignant cell-autonomous immunoevasion strategies to promote tumor formation and progression. In a similar vein, when compared to young patients, aged cancer patients often display attenuated treatment responses to immunotherapy by immune checkpoint blockade (ICB) targeting CTLA-4, PD-1, or PD-L1.²

The aging process entails a profound rewiring of cellular metabolic circuits. Among the best conserved features that define the “aging metabolome” across evolution, two features, namely, (i) impaired mitochondrial activity and (ii) lowered levels of the biogenic polyamine spermidine (Spd), may be interlocked. In particular, there is a sizable body of literature linking oral spermidine supplementation to the prevention and improvement of age-related pathologies. These effects are – at least in part – tied to the induction of autophagy (and often mitophagy for improved mitochondrial quality control) downstream of the inhibition of the acetyltransferase EP300 and/or the hypusination of eIF5a, coinciding with the restoration of homeostatic and effector functions of immune cells including helper T cells³ and B cells.⁴

In their recent work, Tasuku Honjo’s team from Kyoto University shed new light on the anticancer effect of spermidine in aged, tumor-bearing mice treated with ICB therapy, establishing an unprecedented link between supplementation

of exogenous Spd, improved mitochondrial fitness, and enhanced CD8 T cells-dependent antitumor immunity.⁵ In line with the existing literature, the authors detect significantly lower levels of spermidine in the serum and in naive CD8 T cells of old (>1 year) mice than in their young counterparts. Using the colorectal adenocarcinoma MC38 cell line – transplanted into syngeneic immunocompetent aged hosts – the authors observe that Spd administration potentiates the otherwise poor effect of monoclonal antibodies targeting PD-L1 (αPD-L1).⁵ Of note, this effect is accompanied by a reduction in exhaustion markers (and the concomitant increase of effector function) in tumor infiltrating lymphocytes (TILs). It is worth mentioning that the superior anticancer action of the αPD-L1 + Spd combination is independent of mouse age, as it is detectable in young animals. This result is in line with published works, in which Spd administration was shown to enhance the effectiveness of immunogenic chemotherapy and ICB therapy in a CD8-dependent manner.^{6,7} When restimulated *ex vivo*, CD8 T cells isolated from the draining lymph nodes of animals treated with the αPD-L1 + Spd combination exhibit improved memory function, phenocopied by elevated mitochondrial activity as testified by elevated OXPHOS, ATP production, and spared respiratory capacity (SRC). Using naive T cells isolated from aged mice and stimulated *ex vivo* with CD3/CD28 coated beads, the authors demonstrate that the augmentation in ATP levels and SRC induced by Spd are abolished by treatment with the carnitine palmitoyl transferase 1a inhibitor etomoxir, suggesting that Spd stimulates fatty acid oxidation (FAO) in naive CD8 T cells. This result aligns with existing literature connecting extended longevity and ameliorated memory functions of T cells to increased FAO.⁸ From a broader perspective, enhancement of FAO may contribute to the anti-obese functions attributed to Spd in models of diet-induced obesity.⁹ Interestingly, the FAO-stimulating action of

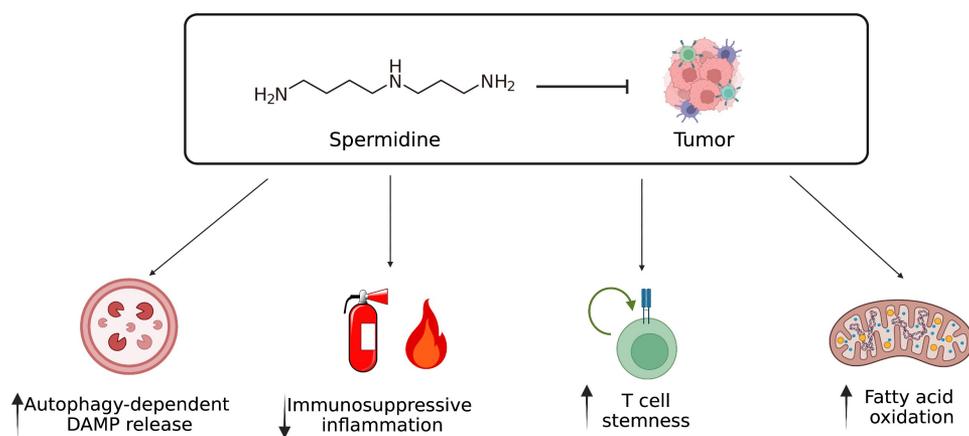


Figure 1 Anticancer effects of spermidine.

Spd is detected as early as 1 hour after Spd treatment and – at least within this temporal window – appears to be independent of eIF5a hypusination or induction of autophagy/mitophagy.

Because Spd rapidly boosts the mitochondrial activity of naive CD8 T cells, the authors postulate that Spd would directly affect the enzymatic activity of rate-limiting enzymes acting in the FAO pathway. Using Spd-coated magnetic nanoparticles incubated with HeLa cells lysate, Honjo's team identifies hydroxyl coenzyme A dehydrogenase subunits a and b (HADHA and HADHB, respectively) – two core components of the mitochondrial trifunctional protein (MTC) complex responsible for long-chain fatty acid oxidation – as the main Spd-binding proteins.⁵ The authors further validate this key finding in intact cells by means of a proximity ligation assay using antibodies targeting Spd and HDAHA/B. By further analyzing the enzymatic kinetics of the HADHA complex, the authors conclude that Spd interacts with HDAHA/B and allosterically activates its enzymatic activities. Due to the fact that the K_m value of Spd for the MTP complex (0.4 μ M) is significantly lower than the K_m of Spd for deoxyhypusine synthase and EP300 – two well-characterized polyamine targets – Honjo's team suggests that MTP activation would represent the earliest molecular event upon Spd treatment. Importantly, the authors report that Spermine (Spm) competitively inhibits the FAO-stimulating effect of Spd, suggesting that Spd/Spm ratio may dictate the outcome of cellular responses after Spd treatment. Finally, Honjo's team utilizes a mouse model in which HADHA expression is conditionally blunted in T cells to confirm that the immunostimulatory effect of SPD+ α PD-L1 combination in young mice relies upon functional HADHA in T cells.⁵

Altogether, the results presented in this study add a further layer of complexity toward the understanding of the pro-health actions of Spd. While the authors suggest that MTP activation would represent the most immediate outcome after Spd supplementation *in vitro*, it is likely that the prominent anticancer properties of Spd *in vivo* are the net result of composite and interconnected events that encompass (i) the activation of the autophagy-dependent release of alarmins from neoplastic cells;⁶ (ii) the avoidance of immunosuppressive inflammation;³ (iii) the promotion of T cell stemness compatible with protracted

immune responses¹⁰ and finally (iv) the improvement in mitochondrial function/FAO in effector T cells (Figure 1).⁵ Moreover, due to the well-documented and direct effect of Spd on epigenetic regulation and gene transcription, it is tempting to speculate that prolonged Spd supplementation would engender additional long-term effects that contribute to the net result, which is improved cancer immunosurveillance.

Acknowledgments

GK is supported by the Ligue contre le Cancer (équipe labellisée); Agence Nationale de la Recherche (ANR) – Projets blancs; Cancéropôle Ile-de-France; Fondation pour la Recherche Médicale (FRM); a donation by Elior; Equipex Onco-Pheno-Screen; Gustave Roussy Odyssea, the European Union Horizon 2020 Projects Oncobiome and Crimson; Institut National du Cancer (INCa); Institut Universitaire de France; LabEx Immuno-Oncology (ANR-18-IDEX-0001); a Cancer Research ASPIRE Award from the Mark Foundation; the RHU Immunolife; Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC Cancer Research and Personalized Medicine (CARPEM). This study contributes to the IdEx Université de Paris ANR-18-IDEX-0001. FC is supported by a Svenska Sällskapet för Medicinsk Forskning (SSMF) Postdoctoral Fellowship (PD21-0071); by Grant from the Alex and Eva Wallström Foundation. FP is supported by a Starting Grant from the Karolinska Institute; Project Grant from Novo Nordisk Fonden (NNF22OC0078239); by Longevity Impetus Grant from Norn Group; by a Starting Grant from the Swedish Research Council (VR MH 2019–02050); by Project Grant from Cancerfonden (21 1637 Pj); by a Starting Grant from Jeanssons Stiftelse. Figure has been created with BioRender.com.

Disclosure statement

GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage. GK has been consulting for Reithera. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics, and Therafast Bio. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis, and metabolic disorders. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. GK's wife, Laurence Zitvogel, has held research contracts with 9 Meters Biopharma, Daiichi Sankyo, Pilege, was on the Board of Directors of Transgene, is a cofounder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota.

Funding

The author(s) reported that there is no funding associated with the work featured in this article.

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