

Serine determines tissue targeted efficacy of PKM2 modulators in atopic dermatitis

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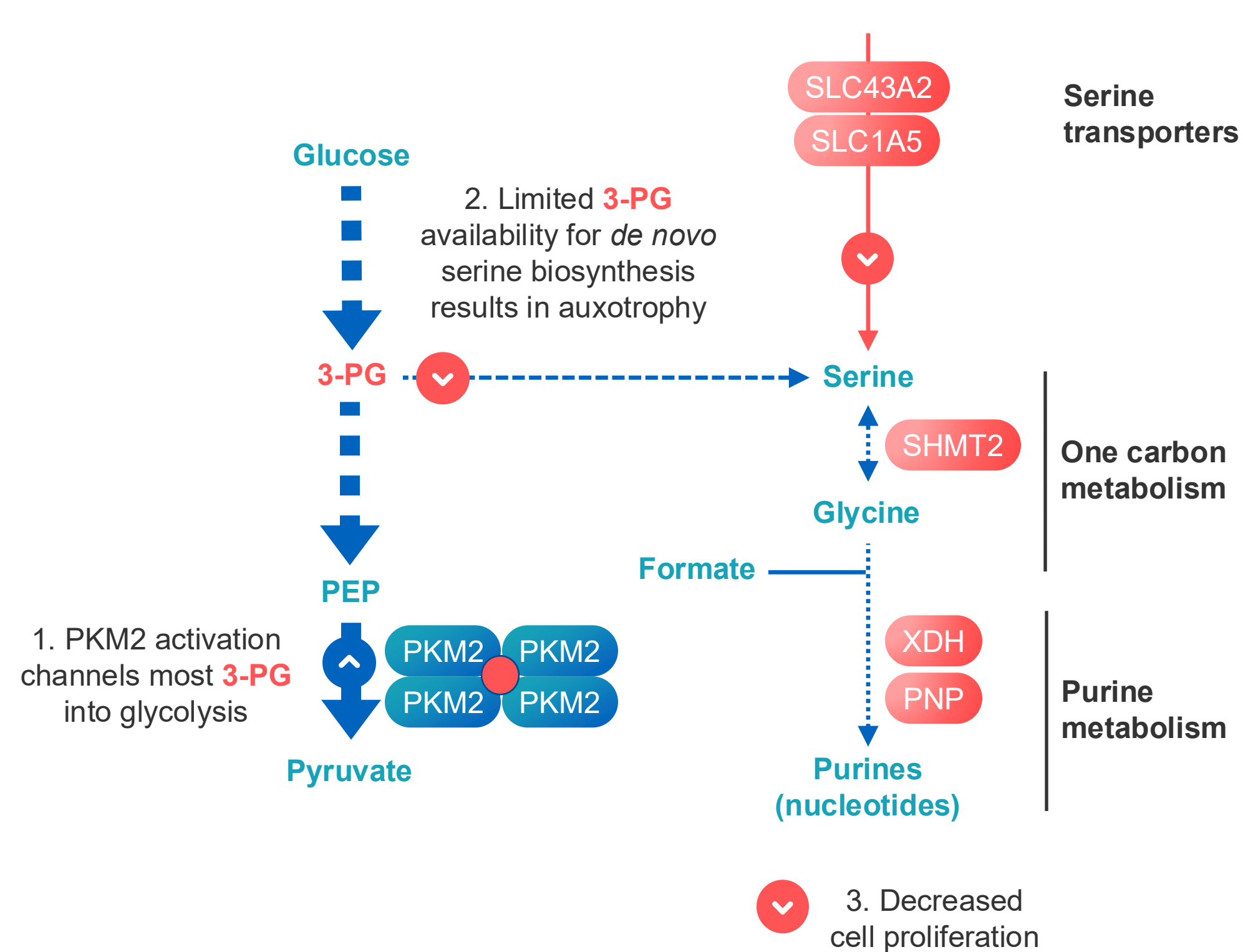
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Introduction

Atopic dermatitis (AD) is a complex, chronic inflammatory, non-contagious skin disease with high unmet need and no curative treatment options. Elevation of serine synthesis enzymes and transporters have previously been described in psoriatic tissues, presenting a potential metabolic vulnerability for therapeutic intervention (Cappello et al., 2022). This study demonstrates that serine is also limiting in AD skin, accompanied by elevation of serine pathway enzymes and transporters. Furthermore, Th2 cells and IgE-expressing B cells play a crucial role in the pathogenesis of AD and these cell types require serine for proliferation and inflammatory responses (D'Avola et al., 2022; Ma et al., 2017). This study describes a novel therapeutic approach to exploit serine limitation in inflammatory tissues by small molecule modulation of a key glycolytic enzyme, pyruvate kinase M2 (PKM2), resulting in anti-inflammatory activity in human Th2 cells and IgE-expressing B cells.

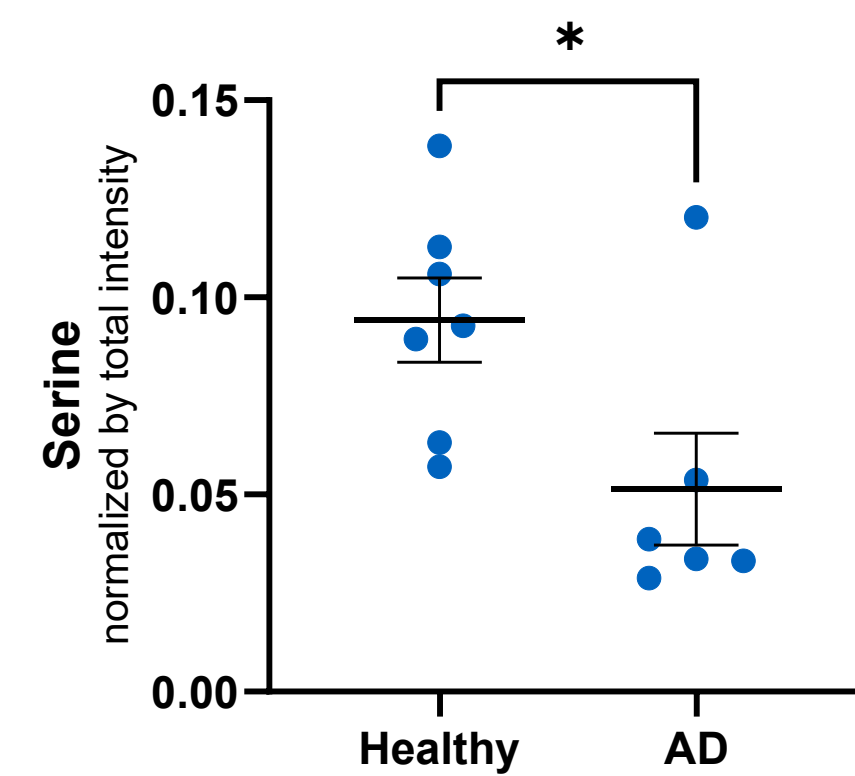
Results

1. PKM2 modulation drives glycolysis and inhibits serine biosynthesis in tissues with high serine demand

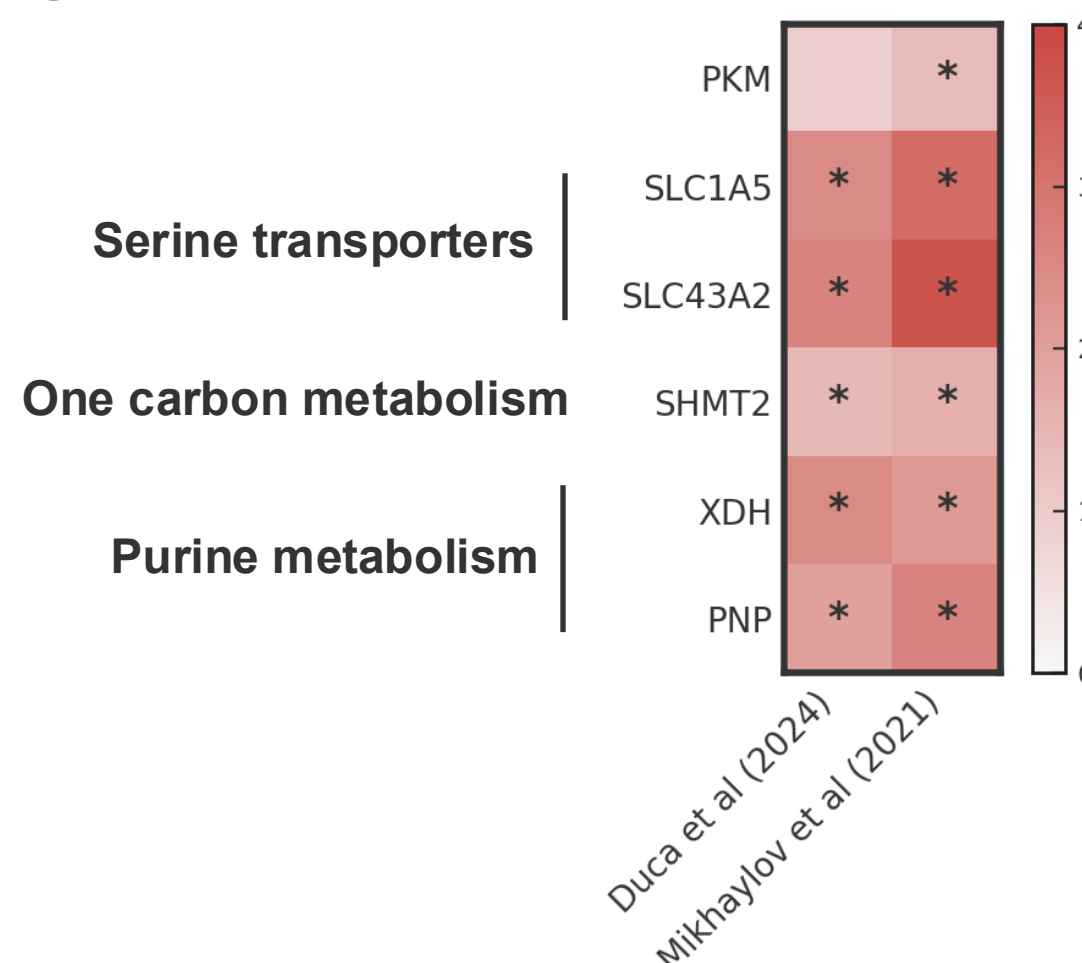


2. High serine demand in lesional AD

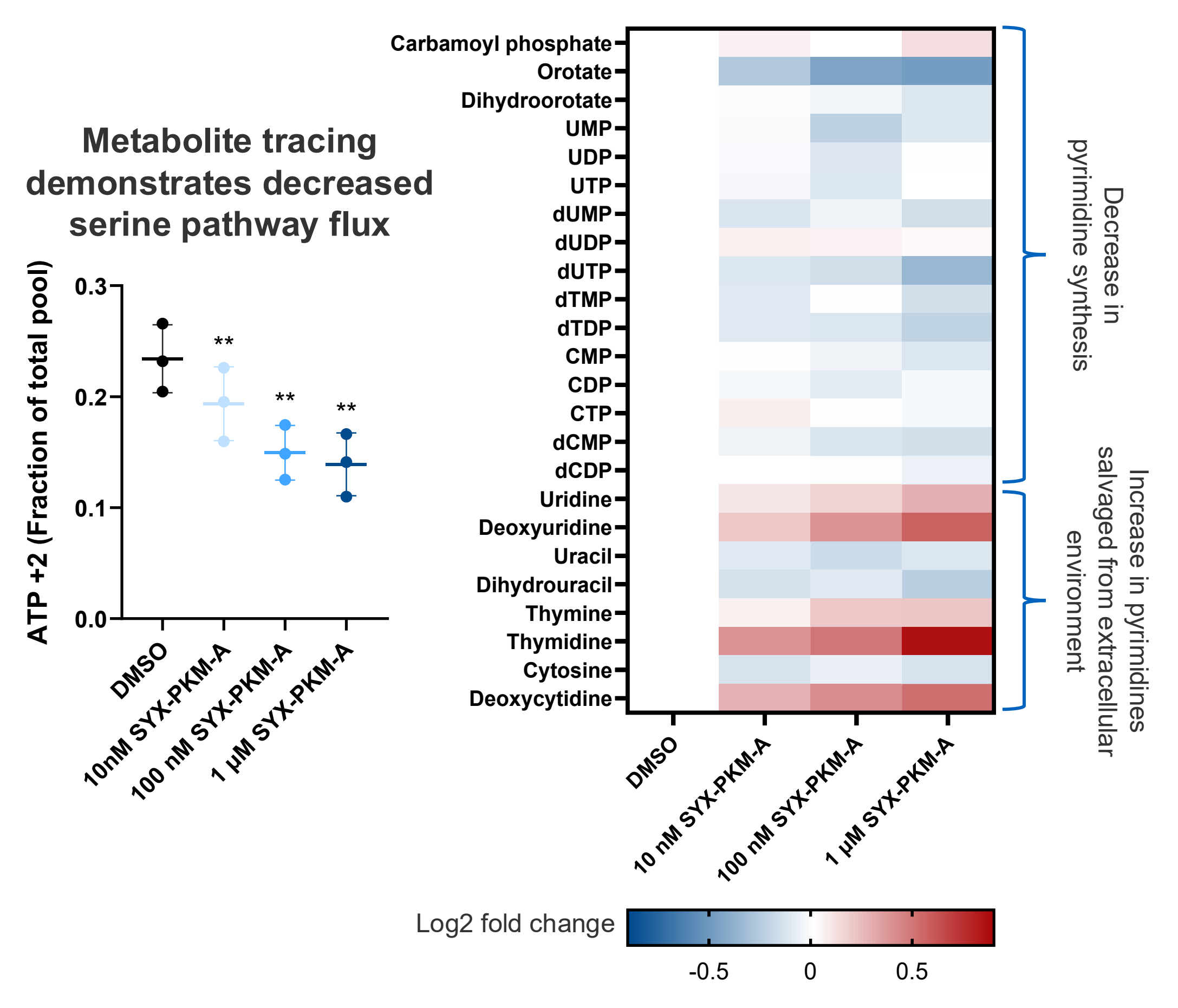
Low serine in AD skin biopsies



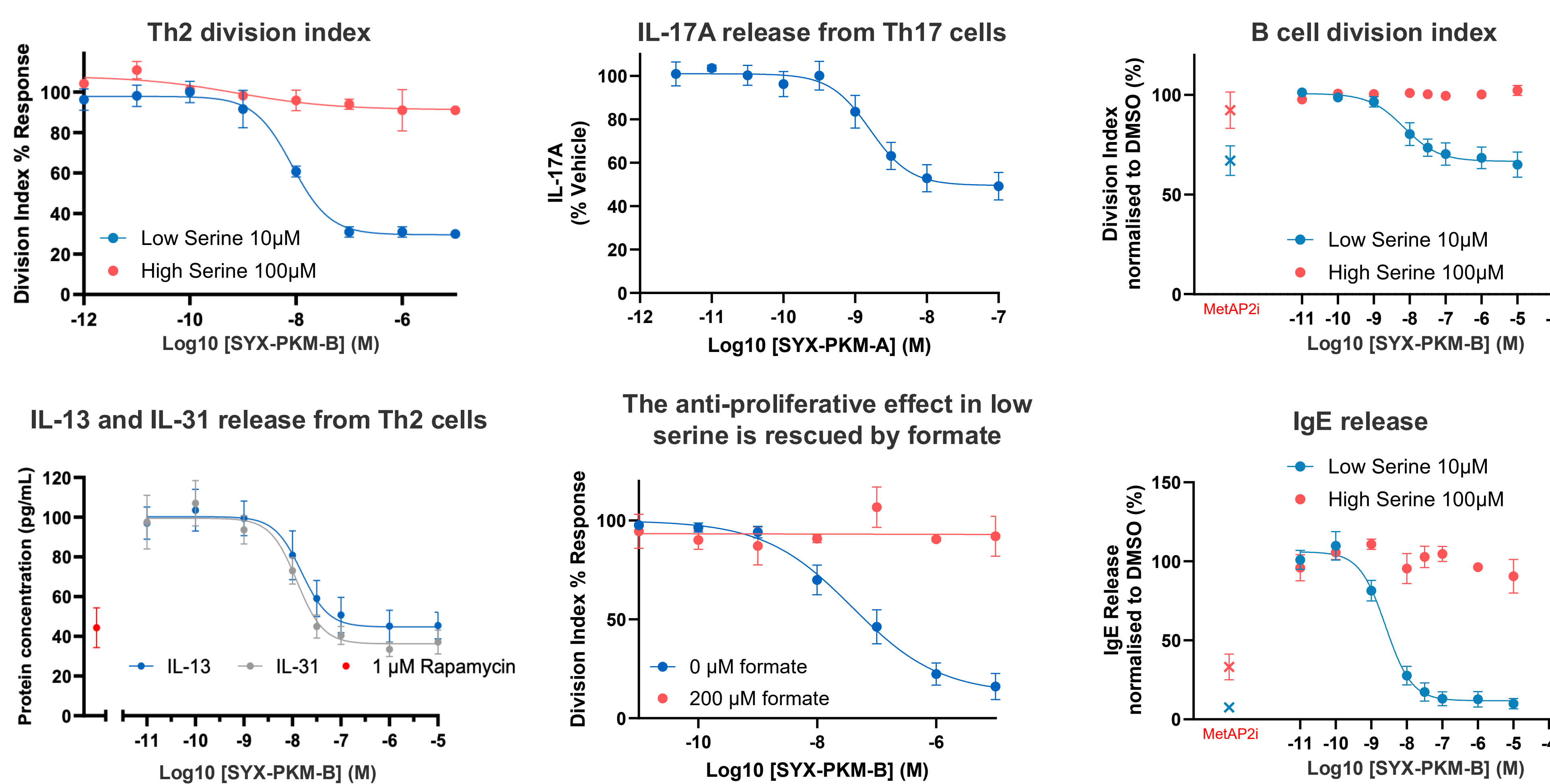
High serine demand in AD skin tape strips



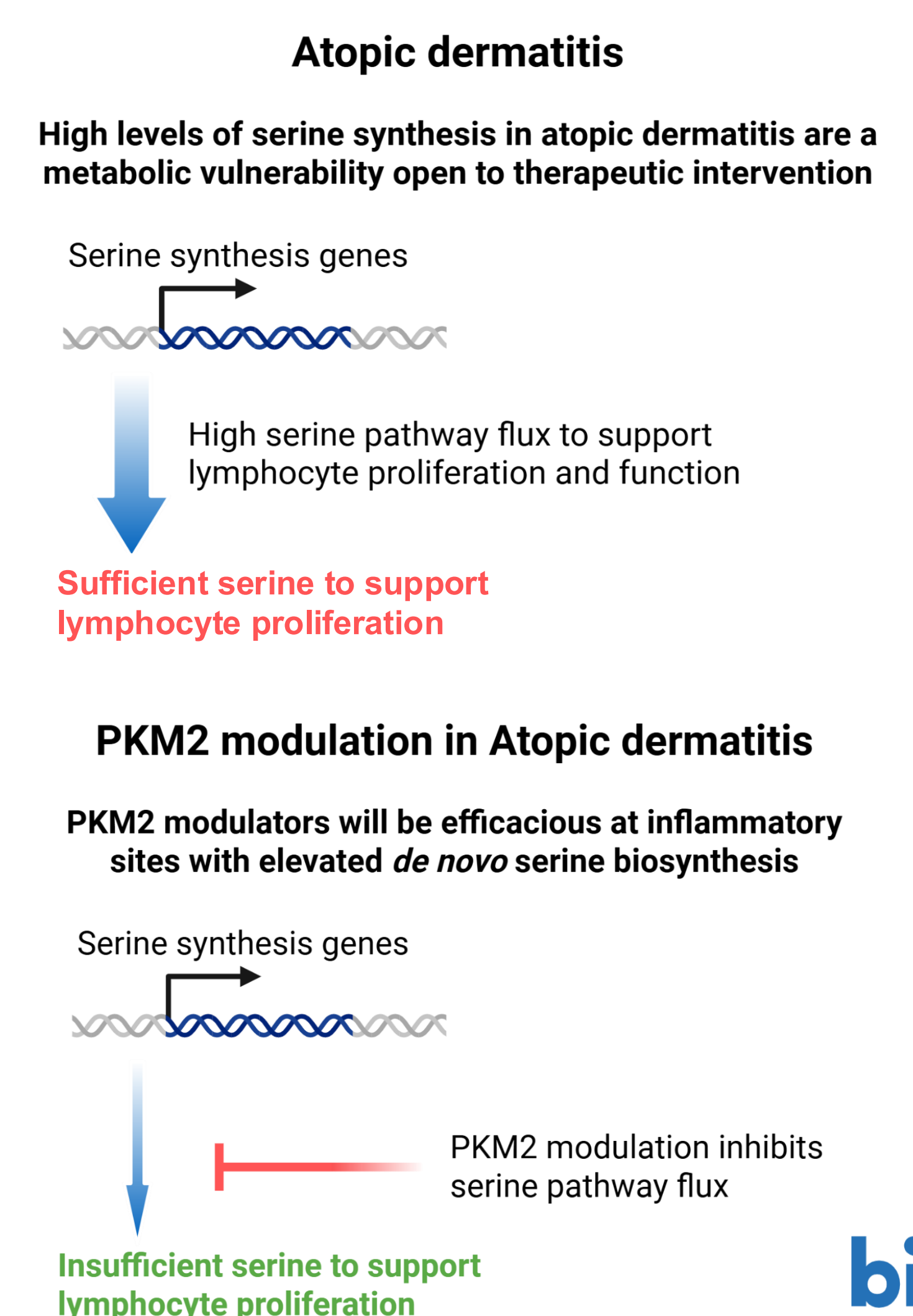
3. PKM2 modulation inhibits serine biosynthesis and downstream pathways in human CD4 T cells



4. PKM2 modulators inhibit Th2, Th17 and B cell function in a low serine environment



6. Serine determines tissue targeted efficacy of PKM2 modulators in atopic dermatitis



1. A. Cappello et al., *Science Advances*, 8, abm7902 (2022).
 2. A. D'Avola et al., *Journal of Clinical Investigation*, 132, e153436 (2022).
 3. E. D. Duca et al., *Allergy*, 79, 80-92 (2024).
 4. E. H. Ma et al., *Cell Metabolism*, 25, 345-357.
 5. D. Mikhaylov et al., *Dermatitis*, 32, S71-S80 (2021).

Conclusions

Serine limitation in AD is characterised by high expression of serine pathway genes and transporters. This presents a potential metabolic vulnerability for therapeutic intervention with a novel PKM2 modulator that inhibits Th2 and IgE-releasing B cells in serine limited conditions. These anti-inflammatory effects of PKM2 modulation were caused by channelling of the glycolytic intermediate, 3-phosphoglycerate towards pyruvate production, reducing carbon flux through serine biosynthesis. The tissue-targeted efficacy of PKM2 modulation at AD inflammatory sites enables a differentiated safety profile. PKM2 modulator, SYX-5219, has recently entered clinical trials in AD (Scan QR code). PKM2 modulation offers an oral, targeted, disease-modifying anti-inflammatory approach, targeting a critical enzyme that regulates cell metabolism. This PKM2 modulator could address the major unmet needs of AD where there are limited treatment options under the current standard of care.

