Trends in
Biochemical Sciences

CellPress
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Spotlight

Metabolic control of RNA splicing by polyamines

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Polyamines are ancient metabolites that support growth, translation, and autophagy. Zabala-Letona *et al.* reveal a new mode of action—'metabolic shielding'—in which polyamines protect phosphorylation motifs in spliceosomal factors. This work links polyamines, for the first time, to alternative splicing, raising new questions for cancer, aging, and beyond.

Polyamines are ubiquitous, polycationic endogenous metabolites linked to cellular growth, proliferation, translation, stress adaptation, chromatin and DNA/RNA interactions, and autophagy [1]. In mammals, putrescine, spermidine, and spermine are the major polyamines, while acetylated intermediates are involved in interconversion, catabolism, export, and excretion. Their pools depend on biosynthesis, catabolism, cellular uptake, dietary intake, the microbiome, and cellular/organismal excretion. Spermidine is the unique aminobutyl-donor for a post-translational modification of the translation factor eIF5A, termed hypusination [2], enabling the translation of hard-to-translate mRNA-encoded motifs, including polyproline stretches [3]. Via eIF5A and other mechanisms, spermidine supports autophagy and mitochondrial function and improves healthspan and lifespan [4]. Consistent with their primordial role in supporting global translation, polyamines have been shown to stabilize ribosomal structures [5], a mechanism likely distinct from the fine-tuning of the translatome via hypusinated eIF5A.

Zabala-Letona *et al.* reveal a broader polyamine–proteome interactome, in which polyamines bind acidic phosphorylatable motifs in spliceosomal proteins and shield them from kinase-mediated phosphorylation [6]. This 'metabolic shielding' mechanism expands polyamine biology from covalent modification and electrostatic stabilization to noncovalent control of protein regulation. Specifically, short-term suppression of *de novo* polyamine synthesis remodeled the phosphoproteome, and enrichment analyses suggested that spliceosomal, mRNA-binding, and mRNA-splicing proteins were affected by phosphorylation changes. In line with this, inhibiting biosynthesis caused reversible and polyamine-rescuable alternative splicing changes, comparable to a splicing program by the U2 snRNP SF3A/SF3B branch-point recognition complex. Accordingly, SF3A3 siRNA or an SF3B inhibitor abolished polyamine depletion-induced splicing alterations.

The study proposes that polyamines act as molecular shields for acidic phosphorylatable motifs in U2 snRNP SF3-subcomplex proteins, particularly within an acidic motif in SF3A3 containing three consecutive phosphorylatable serines. Casein kinases (CK1/CK1α) were experimentally validated to phosphorylate SF3A3, SF3A1, and SF3B2 *in vitro*, and polyamines prevented this phosphorylation. In summary, inhibiting polyamine synthesis exposes SF3 phosphosites to casein kinases, increasing spliceosomal protein phosphorylation and perturbing alternative splicing in cells and tissues.

This metabolite–phosphorylation–spliceosome axis could be relevant for various biological settings. The polyamine dependency of cancer cells locked in a continuously proliferative state mainly stems from the polyamine-dependent control of hypusinated eIF5A and specialized translational programs required to sustain high rates of oncogenic growth and stress adaptation. Accordingly, inhibitors of the polyamine pathway have been trialed in oncology [7]. While classical approaches focused on synthesis inhibition, most notably ornithine decarboxylase (ODC) inhibition by difluoromethylornithine (DFMO), the field has moved toward combined targeting of synthesis and uptake, exemplified by DFMO together with the polyamine transport inhibitor AMXT 1501, which is currently being tested clinically. The metabolic shielding concept suggests that phosphorylation patterns and splicing responses to such treatments should also be considered, as these may affect cancer identity and plasticity, thereby modulating treatment efficacy, especially in combination with other approaches (e.g., polyamine depletion combined with chemotherapy).

Alternative splicing is an important determinant of cell fate decisions and differentiation beyond cancer. Thus, changes in polyamine metabolism across development and lifespan may govern how cells process transcriptional information. This notion suggests that, in addition to being general electrostatic binders, polyamines act as specific regulators of RNA processing, possibly linking metabolite availability to transcriptomic landscapes. This also highlights that noncovalent protein–metabolite interactions may be more important for cellular regulation than currently understood. Interestingly, eIF5A mRNA was recently identified among transcripts undergoing immediate early alternative splicing during T cell activation, and induction of the spliced eIF5A protein variant was sufficient to reduce global translation [8]. Whether this depends on polyamine levels and represents another substrate-feedback mechanism in the pathway remains elusive. Aging is also associated with broad changes in phosphorylation and splicing profiles, alongside altered polyamine metabolism and processes previously linked to polyamines, including proteostasis, inflammation, and stress

responses. While the study does not show that metabolic shielding mediates spermidine-induced geroprotection, it provides this field with a potential new mechanism to test.

Recently, polyamine research has expanded to human supplementation trials. However, the excitement generated by preclinical models of aging and age-associated diseases has been tempered by the recurring pharmacodynamic observation that oral spermidine does not necessarily increase circulating polyamines. Supplementation with spermidine for 7–28 days (40 mg/day) in older men had minimal effects on serum and urinary polyamines, despite exceeding the estimated habitual dietary spermidine intake [9]. Medium doses, such as 6 mg/day, showed clinical effects on immune responses without increasing intracellular concentrations [10]. This has been explained by strong homeostatic control, presystemic conversion, limited bioavailability, or rapid distribution into cellular and tissue compartments that are not captured by current bulk methods. Given the findings by Zabala-Letona *et al.*, biologically relevant spermidine may be more potent when newly synthesized and compartmentalized, rather than taken up and distributed as bulk metabolite pools. Future supplementation studies should, therefore, incorporate isotope tracing, tissue- or cell-specific measurements, and readouts such as phosphoproteomic or splicing signatures.

Whether metabolic shielding extends beyond acidic protein residues in splicing factors to additional proteins, RNAs, or other biomolecular surfaces remains an important question. The next challenge will be to define compartmentalized polyamine pools, including organellar, bound versus free, and polyamine-species-specific pools, and to identify the proteins and other biomolecules they engage with in different settings. Addressing this will require advanced cell biological tools, biosensors, imaging approaches, and low-input targeted metabolomics.

Over decades, polyamines have resisted simple classification and have been linked to a wide range of human diseases, including cancer, neurodegeneration, cardiovascular disease, metabolic disease, and age-associated disorders. Their high demand in many cancers and their implication in aging processes, as well as autophagy regulation, make polyamines attractive yet challenging targets. Metabolic shielding explains why polyamine depletion changes tumor cell behavior beyond just slowing growth. It unmasks phosphorylation sites and rewires the spliceosomal isoform profile. Phosphorylation and splicing signatures could serve as pharmacodynamic readouts of target modulation, something the field currently lacks. In aging research, declining

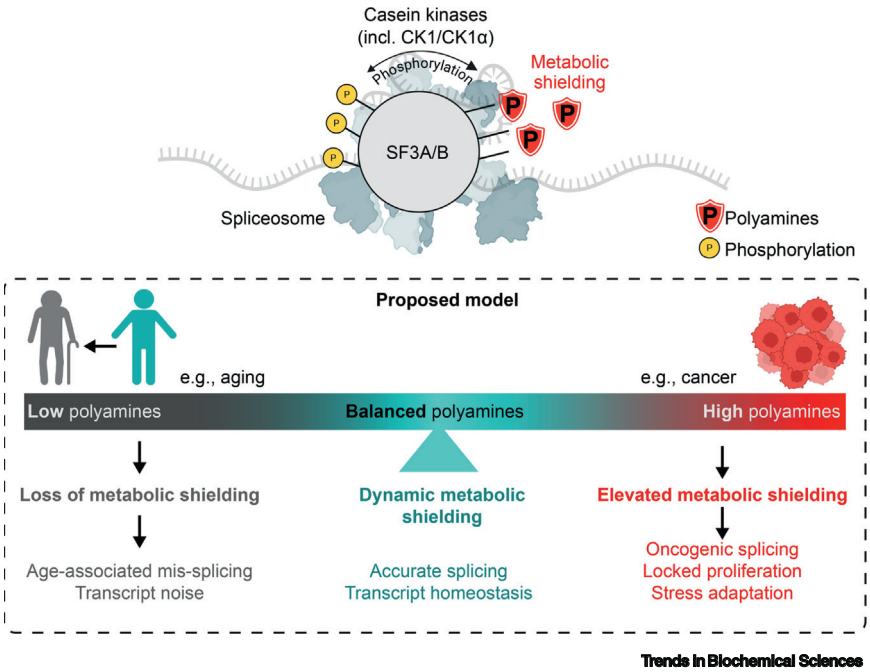

Figure 1. Polyamine-dependent metabolic shielding as a proposed bidirectional regulator of spliceosomal fidelity in health, cancer, and aging. (Top) Zabala-Letona *et al*. showed that polyamines protected acidic phosphorylation motifs on spliceosome components, namely SF3A/B, from casein kinase-dependent phosphorylation. Thereby, polyamine-lowering perturbations shifted the alternative splicing program *in vitro* and *in vivo*. (Bottom) We hypothesize that polyamine profile changes seen during aging and cancer, which are examples of broader disease-related polyamine shifts, contribute to the splicing patterns observed in these conditions. Proposed model: (Bottom–middle) In healthy cells, balanced intracellular polyamine levels maintain a dynamically regulated metabolic shielding state that stabilizes spliceosomal phosphorylation and preserves accurate RNA splicing and transcript homeostasis. This buffering capacity enables adaptive responsiveness during dynamic polyamine changes while preventing excessive spliceosomal instability. (Bottom–right) In cancer settings, constitutively elevated polyamine levels reinforce metabolic shielding and lock the spliceosome into a persistent low-phosphorylation, growth-promoting state. This state promotes oncogenic transcript processing, proliferative signaling, and cellular survival through sustained splicing adaptation. (Bottom–left) During aging, progressive polyamine decline erodes metabolic shielding, resulting in destabilized spliceosomal regulation, impaired phosphorylation control, and reduced splicing fidelity. This loss contributes to aberrant transcript processing, including intron retention and mis-splicing, which are widely observed in aged tissues. This proposed bidirectional model, in which polyamine-dependent metabolic shielding governs spliceosomal regulation across physiological and pathological states, predicts opposing therapeutic interventions in cancer versus aging. The figure was partially created with Biorender.com.

polyamines could lead to reduced shielding, spliceosomal hyperphosphorylation, and aberrant splicing.

Importantly, metabolic shielding could function as a bidirectional switch (Figure 1). In cancer, elevated polyamines lock the spliceosome into a low-phosphorylation, growth-promoting state, whereas in age-associated polyamine perturbations, a progressive decline erodes this protection, contributing to the loss of splicing fidelity observed in aged tissues.

Acknowledgments

This work was supported by the Wellcome Trust (220784/Z/20/Z; to A.K.S.), the Helmholtz Association (REK-0157; to A.K.S.), and Arthritis UK (grant 22617; to G.A.).

Declaration of interests

A.K.S. is a consultant for TLL, The Longevity Labs GmbH, and Oxford Healthspan. G.A. is a consultant for Oxford Healthspan.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (ver. 5.5, OpenAI) and Grammarly (ver. 1.165.1.0) for language and grammar editing. After using these tools/services, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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https://doi.org/10.1016/j.tibs.2026.06.001

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