AURKA targeting: a NEAT approach to halt myeloma

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Multiple myeloma (MM) remains a formidable clinical challenge given its heterogeneous nature and complex pathogenesis. Despite advances in treatment, disease relapses often thwart long-term control, necessitating the development of novel, targeted therapeutic strategies.[1] Long non-coding RNA (lncRNA) have emerged as key players in the regulation of various biological processes, including those involved in the mitotic spindle. They are implicated in the pathogenesis of MM by influencing cell proliferation, apoptosis, invasion, and therapeutic resistance.[2] However, the complex network of lncRNA has left this field only sketchily explored.

In their groundbreaking article published in this issue of *Haematologica*, Puccio *et al.*[3] delve into the regulatory interaction between the lncRNA NEAT1 (nuclear paraspeckle assembly transcript 1) and the serine/threonine kinase AURKA (aurora kinase A), shedding light on their roles in promoting MM cell viability. Through comprehensive multi-omics, transcriptomic, computational, and functional analyses, their study demonstrates that NEAT1 modulates gene networks involved in cytoskeleton dynamics and mitosis by regulating key effectors such as AURKA and TPX2 (microtubule nucleation factor).

Disruption of NEAT1 leads to impaired mitotic spindle assembly,[4] while inhibition of AURKA hinders chromosome segregation, establishing their coordinated roles in maintaining genomic integrity. Excitingly, the combination of NEAT1 silencing and AURKA inhibition exhibits enhanced cytotoxic effects *in vitro*, suggesting a potential synthetic lethality approach[3] (Figure 1). AURKA plays a crucial role in MM pathogenesis by controlling cell cycle checkpoints but the effects of targeting it alone may be circumvented through feedback activation of redundant signaling pathways. The findings by Puccio *et al*. provide a strong rationale for combinatorial targeting, as NEAT1 depletion blocks compensatory pathways while AURKA inhibition eliminates proliferative capacity.[3]

The identified AURKA inhibitors, alisertib and AURKA inhibitor I, have demonstrated manageable safety profiles in phase I clinical trials in MM, supporting their translation into clinical applications.[5] Leveraging established agents with emerging RNA-targeting modalities could expedite the clinical implementation of this research. Importantly, precision targeting of intraclonal vulnerabilities may prove valuable against aggressive and treatment-resistant disease phenotypes. In view of this, the translational relevance of the discovery by Puccio *et al*. is underscored by the correlation of NEAT1 and AURKA co-expression with a poorer prognosis in MM patients, independently of risk stratification models, thus identifying a population of patients with functional high-risk features.[3]

From the clinical standpoint, Puccio *et al*. mention a critical link between AURKA expression and other high-risk MM phenotypes, marked by specific genetic aberrations, namely 1q gain/amplification, 17p deletion, and *MYC/MAF* translocations.[3] Previously, Den Hollander *et al*. discovered that MYC oncoproteins specifically drive aurora A/B kinases in B-cell lymphoproliferative disorders, with inhibition of these kinases showing promise in MYC-driven models.[6] These findings position AURKA as a key therapeutic target, particularly in high-risk MM, and offer hope for effective strategies across a spectrum of malignancies.

In their research Puccio *et al*. employed AMO-1, NCI-H929 and MM1.S human myeloma cell lines,[3] which are derived from pleural, peritoneal extramedullary effusions and peripheral blood, respectively. These biological models recapitulate the enhanced proliferative properties of MM: the enhanced pro-angiogenic property[7] as well as the dynamic and context-dependent interplay with the bone marrow microenvironment conspire to the intrinsic boosted mitotic propensity, disease progression and dissemination.[8] The NEAT1-AURKA axis offers a promising target in this context, as its disruption could address the unique challenges posed by halting unexplored biological circuitries pinpointing to proliferative aggressive disease.

Moreover, it gets even more interesting, as it is evident that genomic stability in MM can be severely compromised.[9] Nonetheless, strategies that efficiently target the dysfunc-

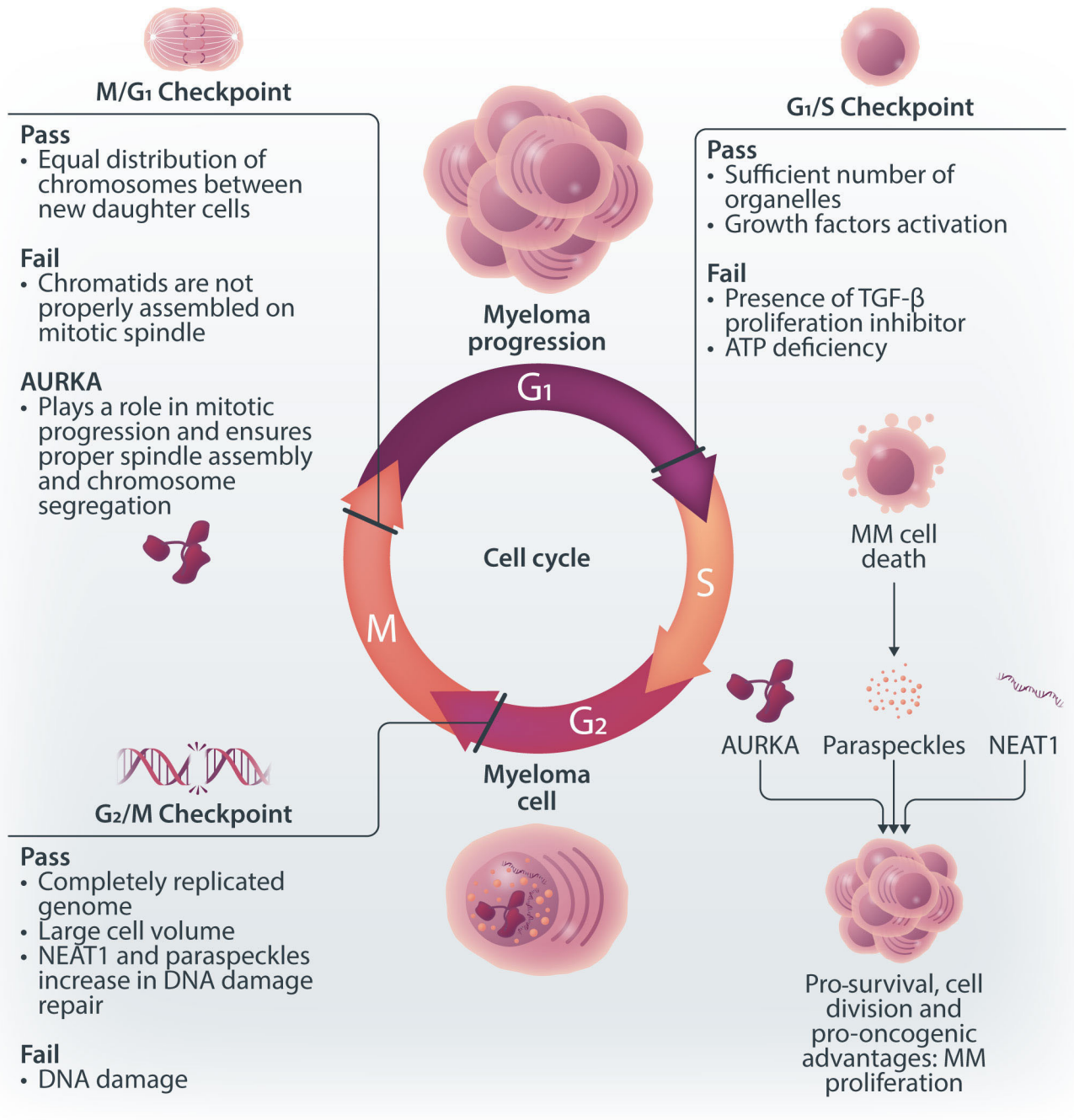

Figure 1. Schematic representation of a novel therapeutic strategy aimed at inhibiting NEAT1 and AURKA to potentially counteract the progression of multiple myeloma. Disruption of the M/G_1 checkpoint prevents the proper assembly of chromatids on the mitotic spindle, thereby arresting the division of multiple myeloma (MM) cells. Intervention at the G_1/S checkpoint impedes the activation of growth factors and organelle production, curtailing cell growth. The inhibition of AURKA's function in mitosis compromises spindle assembly and chromosome segregation.[3] Furthermore, perturbation of the G_2/M checkpoint impairs DNA damage repair mechanisms, culminating in the apoptosis of MM cells. This dual targeting represents a significant advancement in the treatment of MM, exploiting the pro-survival and pro-oncogenic properties of NEAT1[4] and AURKA.[3] AURKA: aurora kinase A; TGF-β: transforming growth factor-beta; ATP: adenosine triphosphate; NEAT1: nuclear paraspeckle assembly transcript 1.

tional spindle-assembly process are scanty. Thus, delving into the regulation of mitosis in MM, it is worth noting that the actors on the scene of mitotic process regulation in MM are sparse. Intriguingly, Favasuli *et al*. showed that inhibiting DIS3 with specific gapmers produced a phenotype akin to that observed in studies on NEAT1.[10] The *DIS3* gene is mutated in approximately 10% of MM patients and DIS3 expression can be influenced by monosomy 13 and del(13q).[10] When DIS3 dysfunction is combined with an impaired spindle-assembly checkpoint, cells may advance through the cell cycle without accurate chromosome separation, resulting in the generation of aneuploid cells, which can facilitate the progression of myeloma.[10] The potential crosstalk between NEAT1, DIS3, AURKA and mitotic control in MM remains a fascinating area that requires further exploration.

Overall, the identified NEAT1-AURKA regulatory axis offers a promising avenue for precision targeting, providing opportunities to disrupt interconnected survival dependencies. By developing optimized regimens that combine AURKA inhibitors with targeted NEAT1 silencing, researchers can potentially achieve enhanced selectivity and overcome resistance mechanisms. Further investigations into NEAT1 isoforms and downstream effectors may reveal additional Achilles' heels that could be the target of interventions within these regulatory pathways. While exploring the impact on tumor-associated cells and immune surveillance, novel opportunities for integrating immunotherapy can be uncovered.[1]

Nonetheless, despite their potential as biomarkers and therapeutic targets, our understanding of lncRNA and mitotic spindle targeting in MM is still limited. The complexity of lncRNA regulatory networks and the need for large-scale studies hinder immediate applications. Further research is required to elucidate the synergistic effects of multiple lncRNA and their interactions with other signaling pathways and proteins, which will enhance our knowledge of MM and potentially lead to more effective treatments.

A particular mention should be reserved for the approach chosen by Puccio *et al.* to validate their results functionally.[3] Their methodology not only identified promising therapeutic targets but also introduces a valuable platform for the study of non-coding molecules. By assaying numerous pathways simultaneously, this holistic approach is of great value for identifying more effective and less toxic cancer therapies, paving the way for rapid translation of therapeutics into clinical practice.

Disclosures

No conflicts of interest to disclose.

Contributions

AGS conceived the editorial. AGS and CB prepared the original draft, reviewed and edited the manuscript and read and agreed to the published version.

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