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Spotlight

Decoding androgen receptor signalling: Genomic vs. non-genomic roles in prostate cancer

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A B S T R A C T

The Androgen receptor (AR) is known to manifest the biological actions of male sex hormones. Androgens are now known to exert a multitude of responses, sometimes contrasting, in physiological and pathological conditions. Several groups have attempted to explain the underlying mechanisms of these varying androgen responses, including the non-genomic actions of androgens. These actions lead to increased activity of pro-proliferative signal transduction pathways, resulting in rapid molecular effects that cannot be explained by the conventional model in which AR functions as a transcription factor to modulate target gene expression [1,2].

This spotlight article examines Safi et al.'s research on the androgen receptor (AR) in prostate cancer, revealing that low androgen levels drive proliferation via non-genomic mechanisms involving AR monomers, while high levels suppress growth through genomic actions with AR dimers. These findings challenge current paradigms and suggest novel therapeutic strategies targeting both AR forms, particularly focusing on the role of AR monomers in cancer progression and treatment resistance.

The hypothesis

In their recent study, Safi et al. sought to explain the non-linear and biphasic responses of prostate cancer cells to androgen, where low androgen levels promote proliferation, while high levels repress growth [3]. The authors hypothesized that prostate cancer cells have distinct AR- centric molecular mechanisms that drive differential responses to varying androgen doses. They were particularly interested in (1) the pro-proliferative effects observed at sub-nano molar androgen doses (castrate levels), and (2) the tumour-suppressive responses seen at high, eugonadal or supra-physiological levels of androgens [4].

Low androgen proliferation mediated by AR's non-transcriptional function

The investigators showed that these non-linear responses were mediated by distinct molecular pathways activated in low versus high androgen conditions. Unexpectedly, the growth promoting effects of low-dose androgens were driven primarily by non-genomic, DNA binding independent action of the AR. This transcription-independent action of AR activates the mTOR signalling to drive pro-proliferative pathways including E2F1 and c-Myc targets. At these low androgen levels, AR did not form dimers which is required for its transcriptional activity, further validating that low levels of androgens promote non-genomic, proliferative action predominantly through the AR monomers.

High-dose androgens suppress proliferation through genomic AR

When comparing low- and high-dose androgen responses, Safi et al. demonstrated that genes upregulated by low-dose androgens were suppressed by high androgen doses. Furthermore, high-dose androgens promoted AR dimerization and nuclear translocation, leading to strong chromatin binding and classical AR target gene activation. This genomic action of the AR in presence of high-dose androgen was associated with suppression of c-Myc expression and the activation of classical AR target genes like prostate-specific antigen and, pushing cells towards a more differentiated cell state.

Therapeutic implications

The study concludes that AR monomers, rather than dimers, are likely responsible for the proliferative effects seen at low androgen doses. These finding challenges current understanding of AR signalling and suggest that AR can drive cell growth via non-genomic pathways, independent of its role as a transcription factor. This revised model proposes that monomeric and dimeric AR mediate distinct biologically responses. It raises important questions about whether the balance between these two forms might allow AR to act as a proliferative monomer in prostate cancer, while functioning as a tumour suppressor dimer in prostate and other cancers, such as breast cancer [5].

Current AR-targeting drugs, like enzalutamide, are designed to block the genomic action of the AR by inhibiting its nuclear translocation and

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dimerization. The findings of this study form the basis for the development of new assays and therapeutic strategies to determine whether AR exists predominantly as a monomer in certain tumours, and whether novel drugs should block both dimeric and monomeric forms of AR. These findings prompt the question of whether truncated forms of the androgen receptor (AR), known as AR variants (AR-Vs), which are enriched in patients who develop resistance to enzalutamide, predominantly arise to perform functions analogous to the monomeric AR, thereby mediating therapy resistance and driving disease progression [6,7].

Another key question arising from these findings is whether current androgen-reducing therapies, which aim to lower androgen levels but often leave residual AR activity, inadvertently allow low-dose androgen signalling to drive cancer progression, even in advanced stages. Future research should test whether investigational AR-targeting compounds can suppress AR monomers, which may play a central role in prostate cancer progression. Additionally, these insights could refine dosing strategies for therapies using high-dose androgens to maximize patient benefit.

Overall, this study by Safi et al. offers valuable insights into the complex, non-linear responses to androgens in prostate cancer and provide distinction between the genomic and non-genomic roles of the AR. In addition to prostate cancer, these findings may have significant implications for treating other cancers in future where AR is now known to play a critical role in driving tumour growth and the inhibitors of AR signalling may soon find their use [8–10].

CRediT authorship contribution statement

Mohammad Asim: Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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