Commentary

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Renin-Angiotensin System Drives Leukemia Progression by Reprogramming the Niche

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We read with great interest the recent study by Pan *et al*. [1], entitled "Inhibiting AGTR1 reduces AML burden and protects the heart from cardiotoxicity in mouse models", published in Science Translation Medicine. In this in-depth study, the authors explored the potential benefit of targeting angiotensin II receptor type 1 (AGTR1) in the treatment of acute myeloid leukemia (AML), mitigating chemotherapy-induced cardiotoxicity. AML treatments are often limited by their toxic effects on the heart, including heart failure and other cardiovascular complications.

The study revealed that the AGTR1-NOTCH1 axis represents a shared molecular pathway between AML and cardiomyocytes, activated in response to chemotherapy. Using human transcriptomic data along with mouse and cellular models, they showed that AGTR1-NOTCH1 axis regulates gene sets associated with stemness and chemoresistance by altering the chromatin-binding landscape of the NOTCH1 intracellular domain when AGTR1 signaling is inhibited. Notably, AGTR1 inhibition reduces AML burden, suggesting an anti-leukemic effect, and provides cardioprotective benefits, shielding the heart from the adverse effects of chemotherapy.

AGTR1 is a key component of the renin-angiotensin system (RAS), which mediates the effects of angiotensin II (Ang II), a potent vasopressor hormone traditionally associated with blood pressure regulation, cardiovascular homeostasis, and fluid balance. Ang II is derived from its precursor protein, angiotensinogen (AGT), synthesized by the liver and cleaved by renal protease renin (REN) to form angiotensin I, which is subsequently converted to Ang II by angiotensin-converting enzyme (ACE/CD143), primarily in the lungs [2]. Beyond its systemic endocrine role, RAS also functions locally in an autocrine and paracrine manner, regulating cellular activity, tissue injury, and regeneration across various organs [3]. Angiotensin peptides act locally as growth modulators, akin to cytokines, influencing cardiac, vascular, renal, and other tissues [4]. All components of the RAS have also been identified in the bone marrow (BM), where they influence hematopoiesis [5,6]. Furthermore, the RAS plays a crucial role in the development of the hematopoietic system during embryogenesis, as reported in the developing avian embryo, where RAS signaling modulates blood island differentiation during the generation of primitive erythroid cells [7].

In line with this, we have previously demonstrated that ACE is a cell surface marker of hematopoietic stem cells (HSC) in human adult BM [8]. Moreover, ACE expression is observed across all developing blood-forming tissues during human ontogeny, including the yolk sac, liver, and the aorta-gonad-mesonephros (AGM) region [9]. Notably, our recent study has also revealed that ACE identifies a specific subset of endothelial cells, known as hemogenic endothelial cells, involved in the emergence of the first HSC during human embryonic development [10]. In addition to ACE, other key components of the RAS, including angiotensinogen, renin, and the AGTR1 and AGTR2 receptors, are also expressed in the AGM region [11]. This expression pattern, observed in both human and mouse embryos, underscores the presence of a local RAS within this embryonic site and suggests its sequential involvement in establishing the definitive hematopoietic system during development [11]. Functionally, *in vitro* perturbation of the RAS through administration of the AGTR1 antagonist Losartan inhibits blood cell generation from dissected AGM region. Conversely, the addition of exogenous Ang II peptide enhances hematopoiesis in culture, significantly increasing the production of immature hematopoietic progenitors [11]. These findings provide compelling evidence that Ang II signaling, via activation of the AGTR1 receptor contributes to the emergence of HSC during ontogeny.

Similarly, the Ang II/AGTR1 axis has been implicated in the proliferation and differentiation of CD34+ hematopoietic progenitors in adult BM, suggesting that a local RAS contributes to the homeostasis of the hematopoietic system in healthy adults [12].

Interestingly, Pan *et al*. [1] reported an overexpression of AGTR1 in circulating AML cells from human patients. Using mouse models, they demonstrated that AGTR1 activation is essential for leukemia development and malignant progression. The authors hypothesized that this phenomenon could involve modifications of the BM niche, a process previously documented in solid tumors [13].

Our findings corroborate these results. By comparing isolated cell populations from the BM of healthy individuals and AML patients, we confirmed the overexpression of AGTR1 in AML blast cells, as described by Pan *et al*. [1]. Additionally, we observed an increased expression of ACE in AML blast cells, consistent with previous reports [14]. Notably, we found that mesenchymal stromal cells from healthy BM, express AGT, ACE, and AGTR1, whereas in AML patients, these cells exhibited significantly elevated levels of AGT and REN expression, suggesting a reprogramming of the BM niche within the leukemic environment.

Compared to healthy individuals, the BM niche in leukemia patients, including both malignant and stromal cells, exhibits a complete overactivated local RAS. This overactivation involves the increased production of the precursor protein (AGT), its enzymatic clevage by REN and ACE, and its response to the resulting active peptides through receptors (AGTR1).

These findings highlight the RAS pathway as a promising therapeutic target with dual benefits for AML patients. It can target leukemic cells and their microenvironment, while also preserving cardiac health. This dual approach has the potential to significantly improve both the quality of life and clinical outcomes for AML patients. Moreover, it paves the way for more effective and less toxic cancer therapies.

Author Contributions

BG, LM, and BL were involved in the literature review and analysis. MT and JNF have made substantial contributions to the manuscript, offering their expertise in all phases of the work. They were instrumental in drafting and revising the intellectual content, ensuring the quality and integrity of the manuscript. Additionally, they provided financial support for the publication and took responsibility for all aspects of the work, overseeing the involvement of the other authors. All authors reviewed and approved the final version of the commentary manuscript. All authors contributed significantly to editorial changes of important content. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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