Angiotensin II Links Cardiovascular Disease With Enhanced Cancer Growth

Benji van Berlo[1], Celine Civati[1], Pierangela Esposito[1], Charles X.L. van Assche[2], Ronny Mohren[2], Alessandra Greco[1], Berta Cillero-Pastor[2,3], Gilles W. de Keulenaer[1], Pieter-Jan Guns[1] and Vincent F.M. Segers[1]

[1]Antwerp University, department PhysioFarmacology
[2]Division M4I – Imaging Mass Spectrometry (IMS), Faculty of Health, Medicine and Life Sciences, Maastricht University.
[3]Department of Cell Biology-Inspired Tissue Engineering, Institute for Technology-Inspired Regenerative Medicine

INTRODUCTION

Several publications have demonstrated that cardiovascular diseases (CVD) such as hypertension and cardiac hypertrophy promote tumor growth in mouse models of breast and lung cancer, suggesting a causal relationship between both diseases. Angiotensin II (ANGII) is a hormone involved in blood pressure regulation, vascular hemostasis and plays a role in the development of cardiac fibrosis and hypertrophy. Moreover, ANGII is cancerogenic by increasing proliferation of several cancer cell types. Here we investigated whether ANGII induced CVD could enhance cancer growth.

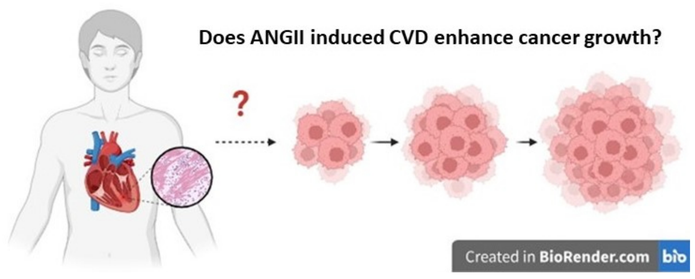
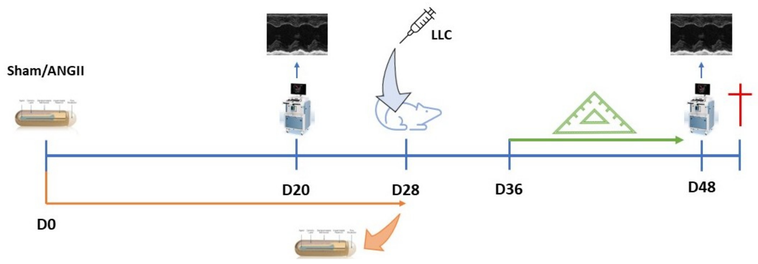


Figure 1. Display of research question

METHODS

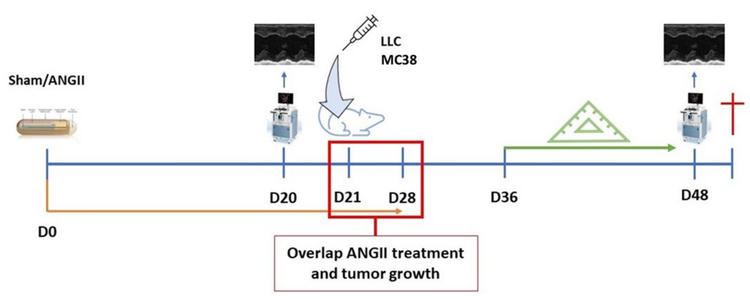
I) Effect of ANGII induced CVD on LLC tumor growth

ANGII (2000ng.kg^{-1}.min^{-1}; 4w) was administered to 10w old male C57B6/J mice using subcutaneous osmotic minipumps. At 4w, 5*10^5 Lewis lung carcinoma (LLC) cells were injected into the right flank. Tumor growth was monitored over 21d using a digital caliper. On day 22, mice were sacrificed for further post-mortem analysis. Figure 2 directly below shows the experimental set-up.



II) Direct impact of ANGII on LLC and MC38 colon cancer growth by concomitant treatment and tumor growth

LLC or MC38 tumor cells were injected at day 21 to have a 7 day overlap period with ANGII treatment. Pumps, cells were placed and injected as mentioned above. Figure 3 directly below shows the experimental overview



RESULTS

I) ANGII induced CVD does not impact LLC tumor growth

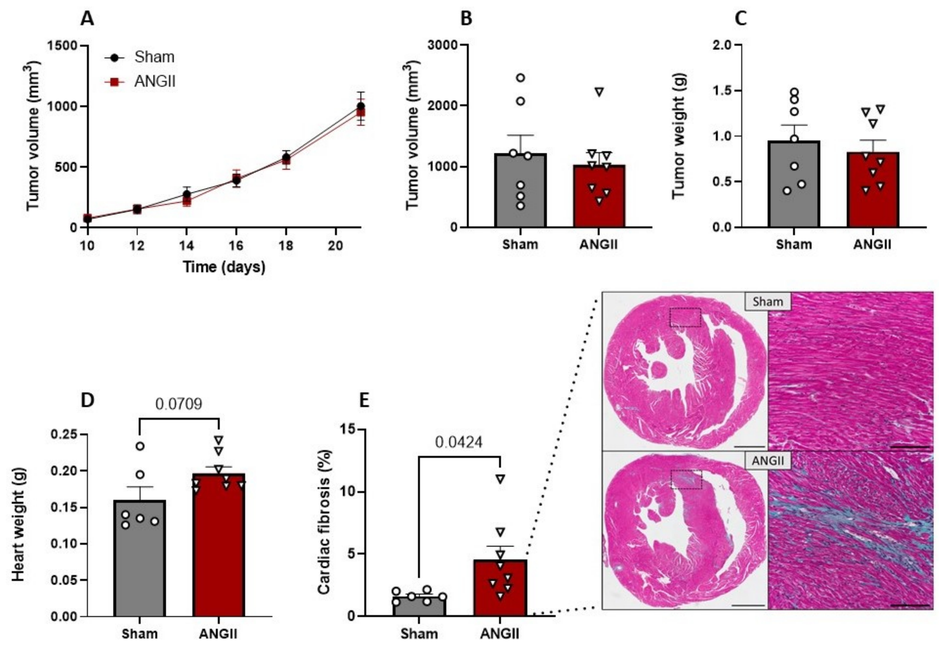


Figure 4. LLC cancer growth in the absence and presence of CVD. A) Tumor progression over time, **B-C)** Tumor volume and weight, **D)** heart weight, **E)** Cardiac fibrosis. Data represents Mean ± SEM.

II) ANGII directly impacts LLC and MC38 tumor growth

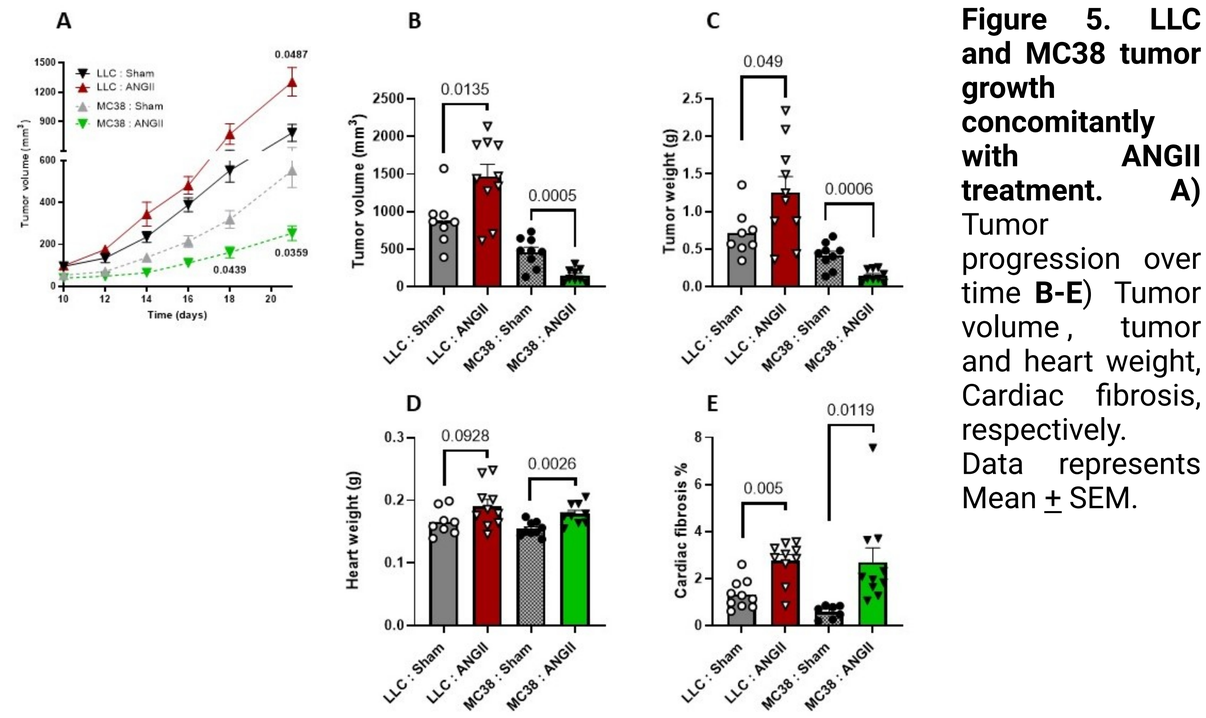


Figure 5. LLC and MC38 tumor growth concomitantly with ANGII treatment. A) Tumor progression over time **B-E**) Tumor volume , tumor and heart weight, Cardiac fibrosis, respectively. Data represents Mean ± SEM.

Proteomic analysis of ANGII treated tumors

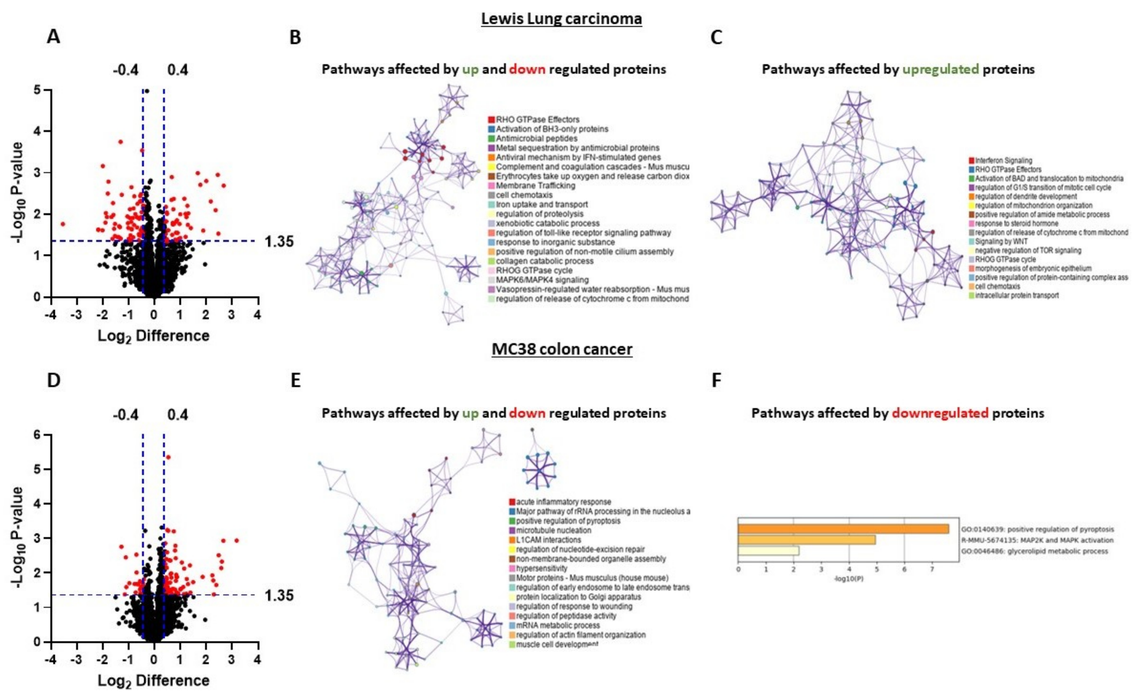


Figure 6. Proteomic analysis of LLC and MC38 tumors treated with ANGII. A and D) Volcano plot displaying differentially expressed proteins in ANGII treated LLC or MC38 tumors. Significance thresholds, P ≤ 0.05 (Log_{10} 1.35) and a Log_2 difference in expression of ± 0.4 are represented by the blue dotted lines. **B-C, E-F)** Pathways affected by up or down-regulated proteins as a result of ANGII administration.

Subpressor and high dose of ANGII administration increase polyp count in APC^{Min} colon cancer mice irrespective of CVD

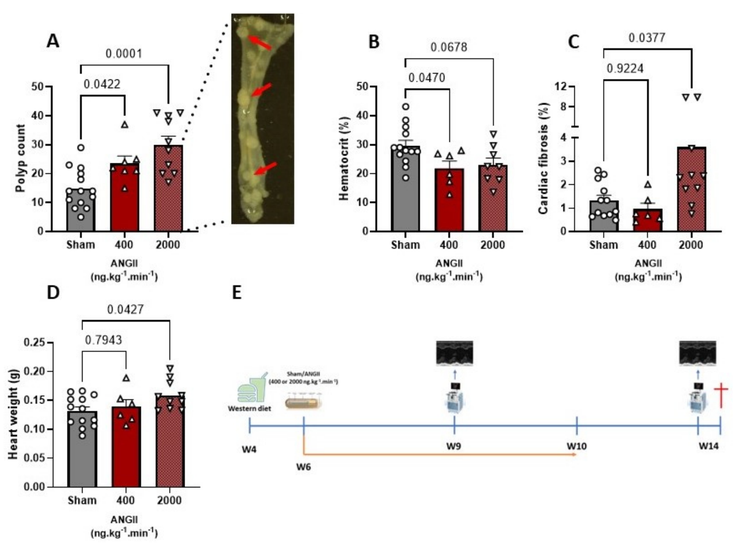


Figure 7. APC^{Min} colon cancer mice treated with subpressor and high dose ANGII. A-E) Polyp count, hematocrit values, cardiac fibrosis, heart weight and experimental set-up, respectively. Data represents Mean ± SEM.

CONCLUSION

Our data suggest a role for ANGII in CVD-enhanced cancer growth, but also that this effect is not universal, illustrated by a differential effect of ANGII on distinct cancer types. Although further investigation is required to unravel the role of ANGII, screening cancer patients with CVD comorbidities for ANGII involvement might be warranted.

Contact information:

Benji.vanberlo@uantwerpen.be

INSPIRE is funded by the EU Horizon 2020 Research and Innovation programme, Marie Skłodowska-Curie Action (858070).