Effects of rA1M on the regulation of apoptotic related genes in kidney medulla after ^{177}Lu-octreotate injection in mice

Klara Simonsson[1], Charlotte Andersson[1], Emman Shubbar[1], Britta Langen[2], Bo Åkerström[3], Magnus Gram[4], Khalil Helou[5], Eva Forssell-Aronsson[1,6]

SAHLGRENSKA CENTER FOR CANCER RESEARCH

UNIVERSITY OF GOTHENBURG

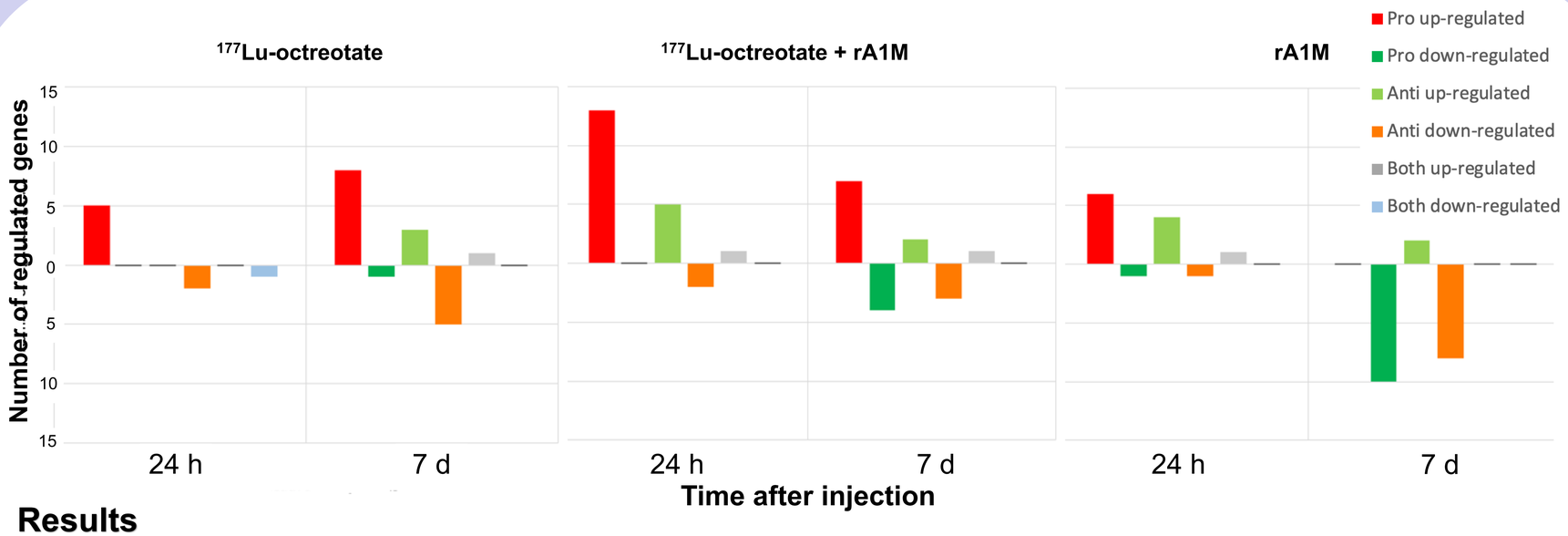
Background

The current treatment schedule using ^{177}Lu-octreotate is seldom curative for patients diagnosed with metastasized neuroendocrine tumours (NETs), where the total administered activity limit is set to protect kidneys from late side effects.

The human recombinant antioxidant α1-microglobulin (rA1M) has been suggested as a potential radioprotector of the kidney. Combining treatment with ^{177}Lu-octreotate and rA1M could enable higher administered activity, and possibly increase the cure rate of patients with NETs.

Aim

Study short term apoptotic effects of rA1M on the transcriptional level in kidney medulla, when used in combination with ^{177}Lu-octreotate.

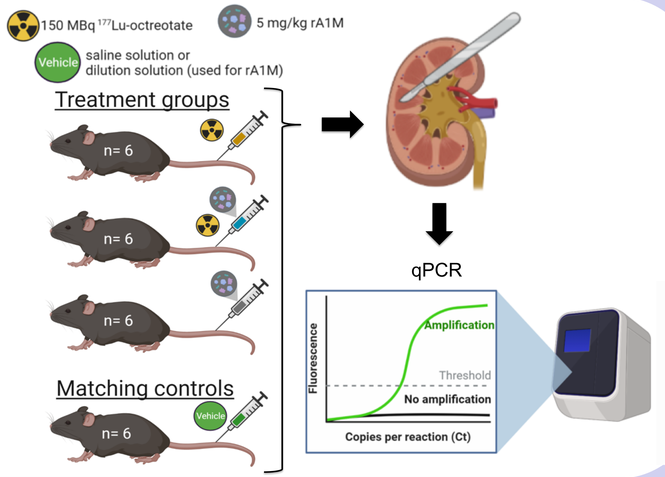


Results

The number of regulated genes (0.66>FC>1.5) in the mice receiving ^{177}Lu-octreotate or rA1M (5 mg/kg) increased with time, unlike the mice receiving ^{177}Lu-octreotate + rA1M, where the number decreased. In the ^{177}Lu-octreotate group the pro-apoptotic genes were mainly upregulated and the anti-apoptotic genes were mainly downregulated, regardless of time. In the combination group (^{177}Lu-octreotate + rA1M), the pro-apoptotic genes were also upregulated at 24 hours, although the number of upregulated anti-apoptotic genes was higher than in the animals that did not receive rA1M. Furthermore, at 168 hours the number of downregulated pro-apoptotic genes were higher in the combination group than in the ^{177}Lu-octreotate only group, and the number of downregulated anti-apoptotic genes was lower. For the animals injected with rA1M the response was mainly up-regulated pro-apoptotic genes at 24 hours, while at 168 hours all regulated pro-apoptotic genes were down-regulated.

Method

In total, 30 C57BL female mice were divided into 3 treatment groups and 2 control groups. Each mouse received two injections. The treatment groups received 150 MBq ^{177}Lu-octreotate, or rA1M (5 mg/kg), or both. The control groups were injected with phosphate-buffered saline or rA1M vehicle solution. Half of animals in each group were killed after 24 hours, and the other half after 7 days. Kidneys were collected immediately and frozen in –80°C. RNA was extracted from kidney medulla. The expression of 84 apoptosis related genes was analysed using RT-qPCR assay.



Conclusion

The results indicate that co-administration of rA1M may decrease the apoptotic response in the kidney medulla in mice after exposure to ^{177}Lu-octreotate.

[1]Dept of Medical Radiation Sciences, Inst of Clinical Sciences, Sahlgrenska Center for Cancer Research, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[2]Dept of Radiation Oncology, Div of Molecular Radiation Biology, UT Southwestern Medical Center, Dallas, USA
[3]Dept of Clinical Sciences, Infection Medicine, Lund University, Lund, Sweden
[4]Neonatology Unit, Dept of Clinical Sciences Lund, Pediatrics, Lund University, Lund, Sweden
[5]Dept of Oncology, Inst of Clinical Sciences, Sahlgrenska Center for Cancer Research, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[6]Medical Physics and Biomedical Engineering, Sahlgrenska University Hospital, Gothenburg, Sweden

For additional information, please contact:
Name: Klara Simonsson
E-mail: gussimkl@student.gu.se

Method figure: Created with BioRender.com.