Overcoming Chemoresistance in Osteosarcoma: The Role of Autophagy

Gabriel Rosa, Beata Burczynska, Britta Stordal, Helen C. Roberts
What are the current issues with osteosarcoma treatment?

Tumour Resistance to Chemotherapy

- Osteosarcoma (OS) is the most common primary bone tumour in paediatric and young adult patients.
- In patients with metastatic or recurrent disease, survival rate has remained unchanged over the past 30 years.\(^1\)
- It is possible that this may be due to chemoresistance.
- A cell survival pathway known as autophagy has been linked to chemoresistance.

Metastatic osteosarcoma 5 year overall survival (%)

What is Autophagy?

What we already know

- Autophagy promotes cell survival by **recycling** damaged components of the cell thus providing the cell with energy.

Stress, starvation, cancer, chemotherapy → Identification of damaged cell machinery → Encapsulation of damaged cell machinery → Breakdown & recycling of damaged cell machinery

**Autophagosome** **Autolysosome**
Some studies have shown that cancer cells use autophagy to survive during chemotherapy using drugs like doxorubicin and cisplatin.

In OS the role of autophagy is still unclear, with autophagy promoting either cell death or survival depending on the grade/type of tumour and the drug used.²

Our End Goals

Scientific End Goals
Define the role of autophagy in controlling chemoresistance in different grades of OS.

Patient Value End Goals
Provide proof of concept data that pharmaceutical regulation of autophagy alters OS cell properties.
Measuring Autophagy

Activation of LC3-II: A key step in the autophagy process

- Stress, starvation, cancer, chemotherapy
- Identification of damaged cell machinery
- Encapsulation of damaged cell machinery
- Breakdown & recycling of damaged cell machinery

Options:
- Cell death
- Cell survival
**Autophagy Activation in Osteosarcoma**

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<tr>
<th>NORMAL BONE</th>
<th>GRADE 2</th>
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**LC3-II expression in osteosarcoma tumour biopsies**

5) Rosa et al., unpublished data; Osteosarcoma tissue microarray – AMSBIO
Autophagy Activation in Osteosarcoma

LC3-II expression in osteosarcoma tumour biopsies

5) Rosa et al., unpublished data; Osteosarcoma tissue microarray – AMSBIO
Autophagy Activation and Survival in Osteosarcoma

Data obtained from R2 Genomics Analysis and Visualization platform; dataset GSE42352; Kujier et al., 2012; n = 53

A) Overall Survival

B) Metastasis-free Survival

Low LC3-II

High LC3-II

P = 0.039

P = 0.0095
What is the role of autophagy in chemoresistance in different grades of osteosarcoma?

In vitro analysis of key components of the autophagy pathway.
What is the role of autophagy in chemoresistance in different grades of osteosarcoma??

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<th>HOS-143B</th>
<th>MG-63</th>
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Doxorubicin and cisplatin induce the formation of LC3-II punctate. More LC3-II punctate formed in HOS143B cells.

*Rosa et al., unpublished data*
What is the role of autophagy in chemoresistance in different grades of osteosarcoma??

Doxorubicin and cisplatin induce the formation of LC3-II punctate

More LC3-II punctate formed in HOS143B cells

Rosa et al., unpublished data
What is the role of autophagy in chemoresistance in different grades of osteosarcoma?

*What is the role of autophagy in chemoresistance in different grades of osteosarcoma??*

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**HOS-143B**

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*Increased clearance of p62 with doxorubicin and cisplatin*

*Increased conversion of LC3-I to LC3-II with doxorubicin and cisplatin*

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**MG-63**

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*What is the role of autophagy in chemoresistance in different grades of osteosarcoma??*
Modulating autophagy in osteosarcoma

Inhibiting autophagy with chloroquine reduces the IC50 of cisplatin in HOS-143B cells

Chloroquine

Rosa et al., unpublished data
Defining the role of autophagy in controlling chemoresistance in different grades of OS.

- Aggressive OS tumours express high levels of autophagy that could relate to their growth, metastatic potential and chemoresistance.
- Doxorubicin and cisplatin can induce autophagy in OS cell lines (with a higher level of autophagy induction in more metastatic cells).
- Autophagy inhibition can influence response of OS cells to chemotherapy. Genetic targeting of autophagy will provide better insight.
Thanks...!

Dr Britta Stordal  Dr Beata Burczynska  Gabriel Rosa