Dermatan sulfate mitigates radiation-induced oral mucositis (mouse) – biological mechanisms

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Oral mucositis in HNC patients

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Research strategy

1. functional analyses –
   - effects on ulcer incidence, latency and duration

2. mechanistic analyses –
   - protein expression during 10 x 3 Gy +/- DS
Effect of DS: mucositis incidence

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Effect of DS: mucositis latency

Drug administration interval (first / last day)

* p < 0.05
** p < 0.01
*** p < 0.001
**** p < 0.0001
Effect of DS: mucositis duration

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Histological / immunohistochemical analyses of RT- and DS-induced cell signaling changes

- Radiation schedule:
  - 3 Gy
  - No irradiation

- DS treatment:
  - Daily DS treatment (4 mg/kg)

- Sacrifice schedule:
  - Sacrifice of groups of mice
    - (n=5 per experimental group)
Effect of DS on epithelial cellularity and proliferation

DS administration: from day -3 to 11

DS increased cell numbers without stimulating proliferation
Effect of DS on adherense junctions

β-catenin

Fraction of β-catenin membrane positive cells (%) / germinal epithelium

E-cadherin

Fraction of e-cadherin positive cells (%) / germinal epithelium

germinal layer

functional layer

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Effect of DS on tight junctions

Claudin-1

Fraction of claudin-1 positive cells (%) / germinal epithelium

Occludin

Fraction of occludin positive cells (%) / germinal epithelium

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Occludin expression during 10 x 3 Gy wo/with DS treatment

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<th>IR+DS</th>
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<td>0 Gy</td>
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<td>10 x 3 Gy</td>
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Effect of DS on inflammation

- **IL-1β**-pos. macrophages
  - DS mitigates oral mucositis

- **NF-κB p50**
  - Fraction of NF-κB p50 pos. cells (%), germinall epithelium

- **IR**
- **IR+DS**

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Effect of DS on hypoxia

GLUT-1

Fraction of GLUT1 pos. cells (%), germinial epithelium

Days after onset of irradiation

HIF-1α

Fraction of HIF-1α pos. cells (%), germinial epithelium

Days after onset of irradiation

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Conclusion

- significant amelioration of OM
  - incidence
  - latency
  - duration

- NO enhanced proliferation
- increased cellular junctions
- reduced inflammation
- reduced hypoxia

Potentially suitable compound for an OM treatment strategy
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and many others ......