Tumor microenvironment imaging: Benefits of multimodality to study chondrosarcoma

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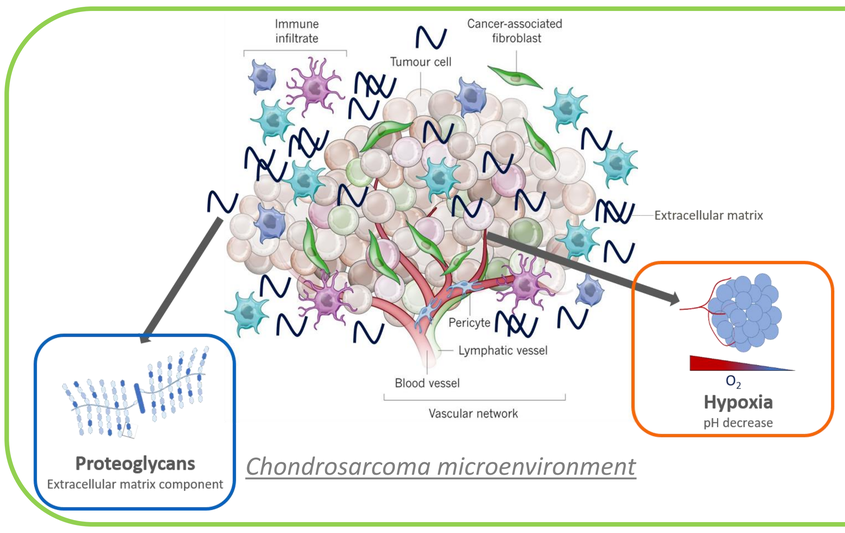


Chondrosarcoma microenvironment

CONTEXT

Chondrosarcoma (CHS) is a malignant cartilaginous tumor representing the most common primary bone cancer in adults (https://www.cancer.org/cancer/bone-cancer/about/key-statistics.html, *American Cancer Society Web site*, 2021). Due to its dense chondrogenic extracellular matrix and hypoxic environment, CHS is highly resistant to conventional chemotherapy and radiation (Nazeri E *et al.*, *Crit Rev Oncol Hemat,* 2018). Development of multimodal imaging to characterize and map *in vivo* CHS microenvironment is fundamental for specific diagnosis and personalized therapy.

In this context, we proposed to combine the resolution of chemical exchange saturation transfer (CEST) MRI with nuclear imaging sensitivity to improve CHS microenvironment understanding (Autissier R *et al.*, *Magn Reson Med*, 2021).

METHODS

Swarm rat CHSs were implanted subcutaneously in NMRI nude mice (n=10).

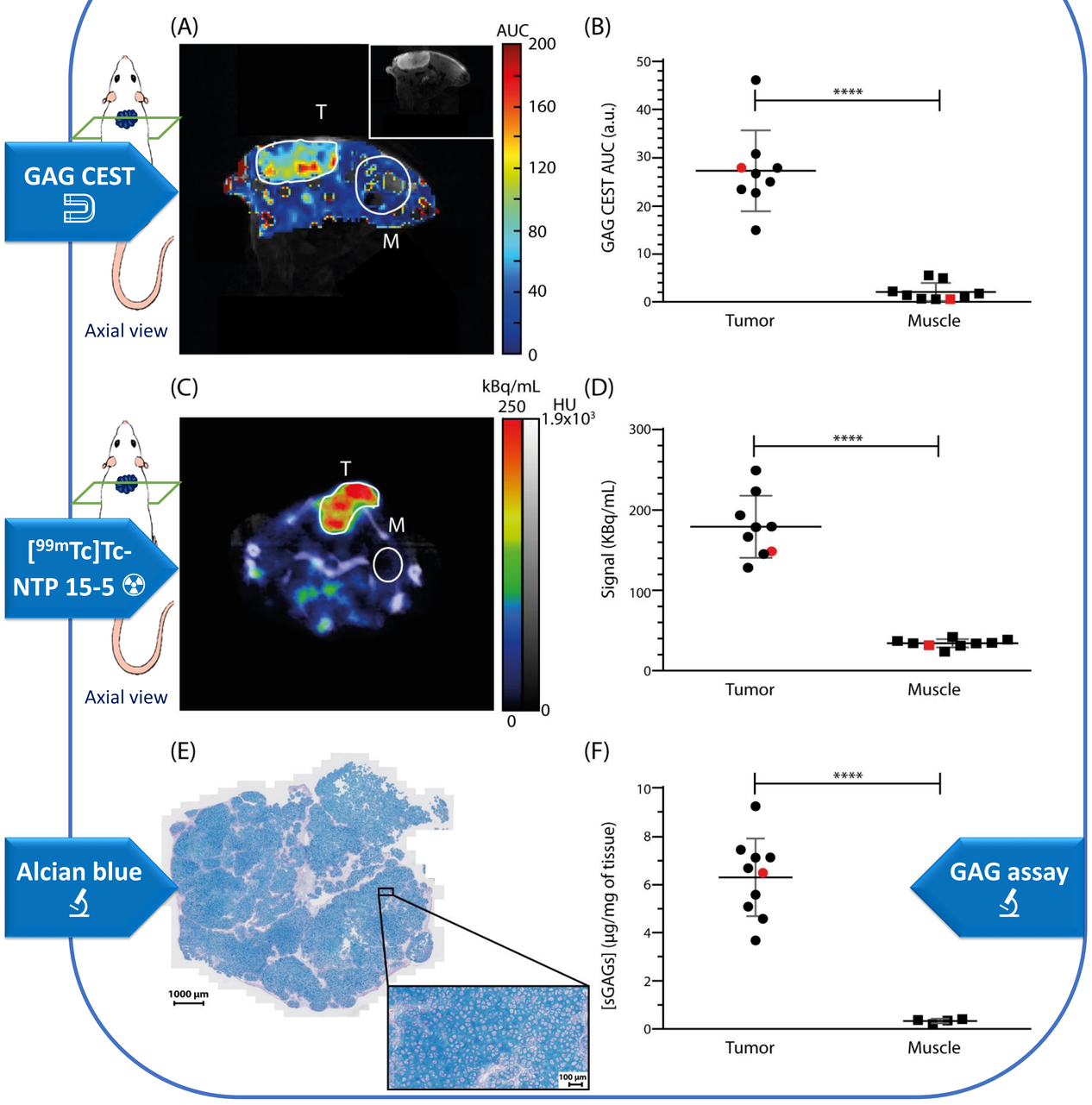
When tumors were measurable (12-16 days post-transplant), mice were imaged by CEST MRI (Dou W *et al.*, *Quant Imaging Med Surg*, 2019). Proteoglycans, the main component of chondrogenic extracellular matrix, were quantified by GAG CEST contrast. Guanidyl- and APT CEST contrasts were combined to characterize acidic pH, as hypoxia reflect.

These two features, proteoglycans and hypoxia, were assessed in parallel by nuclear imaging with [^{99m}Tc]Tc-NTP 15-5 SPECT imaging (Peyrode C *et al.*, *Sarcoma*, 2011) and [^{18}F]-FMISO PET imaging (Rajendran JG *et al.*, *Clin Cancer Res*, 2004), respectively.

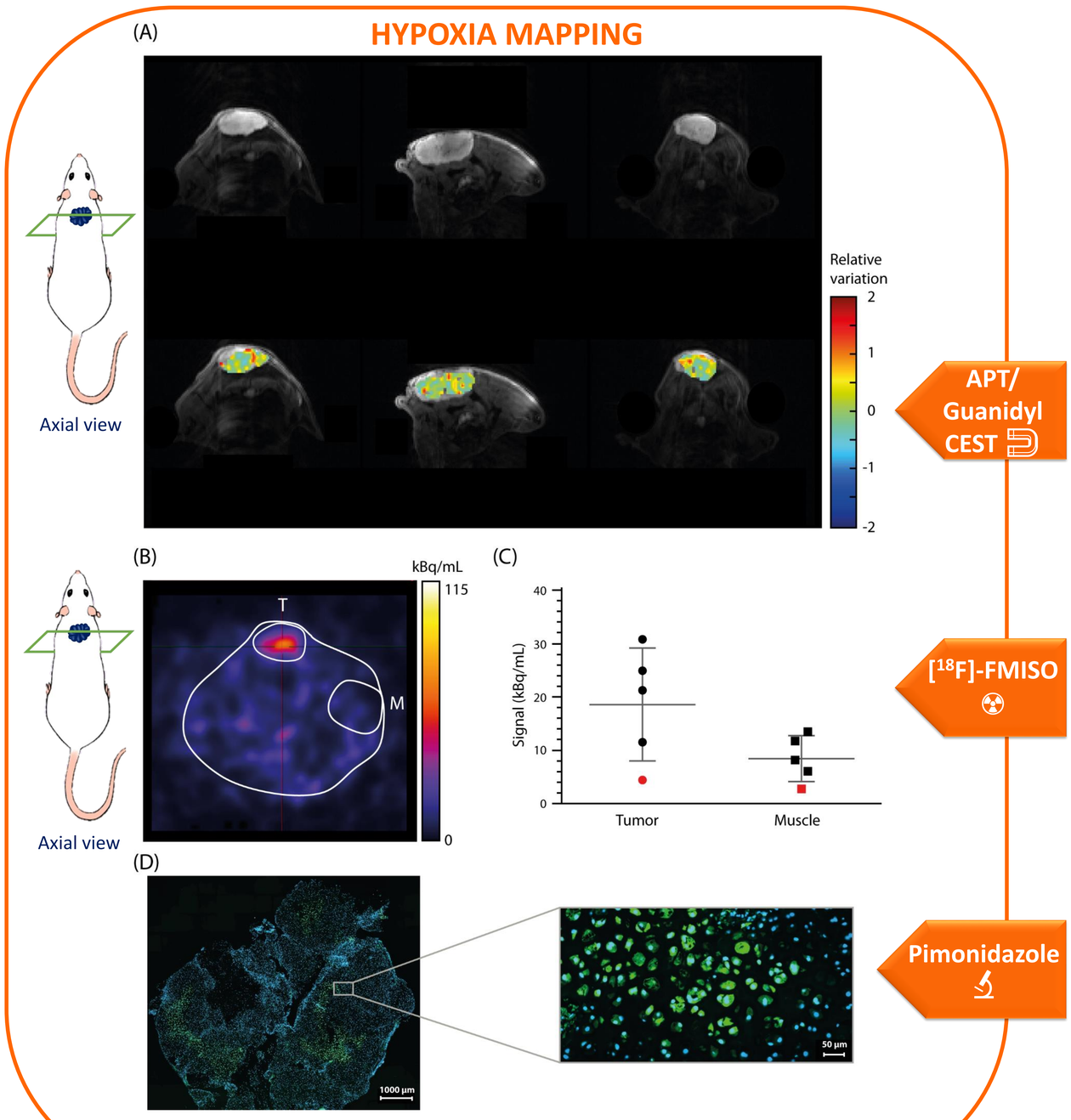
Data were also completed by *ex vivo* analyses of tumor and muscle proteoglycans (Alcian blue stain and biochemical assay with dimethylmethylene blue) and hypoxia (pimonidazole immunofluorescence).

RESULTS

PROTEOGLYCAN MAPPING



HYPOXIA MAPPING



CONCLUSION: The results from CEST MRI, nuclear imaging and *ex vivo* analyses were in agreement and highlighted a rich proteoglycan extracellular matrix and a heterogeneous hypoxic tumoral microenvironment for Swarm rat CHS xenograft in mice.

This study emphasizes the role of multimodal imaging to characterize tumor phenotypes resistant to treatments and allows a better understanding of the relationship between tumor cells and their environment.

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