TUMOR MICROENVIRONMENT IMAGING: BENEFITS OF MULTIMODALITY TO STUDY CHONDROSARCOMA

Roxane Autissier, ; Leslie Mazuel, Elise Maubert, Jean-Marie Bonny, Philippe
Auzeloux, Sébastien Schmitt, Amidou Traoré, Caroline Peyrode, Elisabeth
Miot-Noirault, Guilhem Pagés

HAL Id: hal-03334052
https://hal.inrae.fr/hal-03334052

Submitted on 3 Sep 2021

TUMOR MICROENVIRONMENT IMAGING: BENEFITS OF MULTIMODALITY TO STUDY CHONDROSARCOMA

Roxane Autissier[1,2,3] ; Leslie Mazuel[1,2,3] ; Elise Maubert[2] ; Jean-Marie Bonny[1,3] ; Philippe Auzeloux[2] ; Sébastien Schmitt[2] ; Amidou Traoré[1,3] ; Caroline Peyrode[2] ; Elisabeth Miot-Noirault[2] ; Guilhem Pagés[1,3]

[1]INRAE, UR QuaPA,F-63122 Saint-Genès-Champanelle, France ; [2]Universite Clermont Auvergne, INSERM, U1240 Imagerie Moléculaire et Stratégies Théranostiques, F-63000 Clermont-Ferrand, France ; [3]INRAE, ISC AgroResonance, F-63122 Saint-Genès-Champanelle, France

INTRODUCTION: Chondrosarcoma (CHS) is a malignant cartilaginous tumor representing the most common primary bone cancer in adults.[1] Due to its dense chondrogenic extracellular matrix and hypoxic environment, CHS is highly resistant to conventional chemotherapy and radiation.[2] Development of multimodal imaging to characterize and map *in vivo* CHS microenvironment is fundamental for specific diagnosis and personalized therapy. In this work, we proposed to combine the resolution of chemical exchange saturation transfer (CEST) MRI with nuclear imaging sensitivity to improve CHS microenvironment understanding.[3]

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.[4] 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-NTP 15-5 SPECT imaging [5] and ^{18}F-FMISO PET imaging [6], respectively. Data were also completed by *ex vivo* analyses of proteoglycans (Alcian blue stain and biochemical assay with dimethylmethylene blue) and hypoxia (pimonidazole immunofluorescence).

RESULTS/DISCUSSION: For extracellular matrix assessment, a proteoglycan concentration-related map was established with GAG CEST contrast showing more intense areas in the tumor than in the muscle (AUC =27.29 ± 8.38 vs 2.15 ± 1.88, respectively; $P < 0.0001$) (Fig 1). Similarly, a significant ($P < 0.0001$) radiotracer uptake was observed by nuclear imaging with ^{99m}Tc-NTP 15-5 within tumoral tissue (179.38 ± 38.39 kBq/mL) as opposed to muscle (35.07 ± 5.17 kBq/mL). These results were supported by biochemical assay (6.33 ± 1.60 µg/mg vs 0.41 ± 0.09 µg/mg, respectively; $P < 0.0001$). Considering hypoxia, a small discrepancy was observed between CHS and muscle with ^{18}F-FMISO PET imaging. Interestingly, with Guanidyl and APT contrast, the weakly hypoxic status of the CHS was explained by a heterogeneous acidic pH distribution within the tumoral tissue (Fig 1). Moreover, immunofluorescence with pimonidazole evidenced a weak staining within tumor mainly localized in the center of CHS lobules.

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.

Figure 1 : *In vivo* CEST MRI maps obtained during the same acquisition; M: Muscle; T: Tumor

[1] *Key Statistics for Bone Cancer: Key Statistics About Bone Cancer*. American Cancer Society Web site. Available at: https://www.cancer.org/cancer/bone-cancer/about/key-statistics.html. Updated January 12, 2021
[2] Nazeri E, Gouran Savadkoohi M, Majidzadeh-A K et al., 2018, Crit Rev Oncol Hematol. 131:102-109, doi: 10.1016/j.critrevonc.2018.09.001
[3] Autissier R, Mazuel L, Maubert E et al., 2021, Magn Reson Med. 86(2):1008-1018, doi: 10.1002/mrm.28781
[4] Dou W, Lin CE, Ding H et al., 2019, Quant Imaging Med Surg. 9(10):1747-1766. doi: 10.21037/qims.2019.10.03
[5] Peyrode C, Gouin F, Vidal A et al., 2011, Sarcoma. 2011:691608, doi: 10.1155/2011/691608
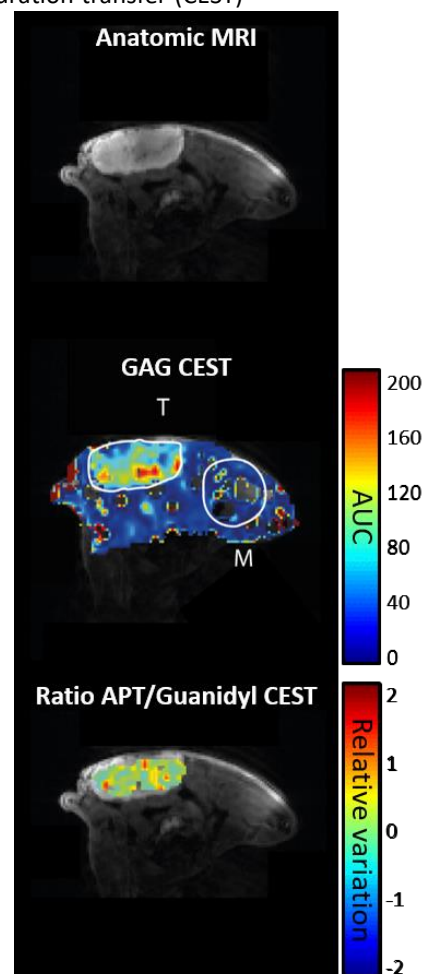[6] Rajendran JG, Mankoff DA, O'Sullivan F et al., 2004, Clin Cancer Res. 10(7):2245-52. doi: 10.1158/1078-0432.ccr-0688-3.