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Analysis of the role of the intratumoral microbiota on soft tissue sarcoma cell metabolism and migration

Scientific Background

Soft tissue sarcomas (STS) are mesenchymal malignancies with an estimated annual incidence in Europe for all histotypes together of 4-5/100000/year. The most common histotypes (liposarcoma and leiomyosarcoma) have an incidence of <1/100 000/year (Gronchi et al., 2021). STSs account for over 20% of all paediatric solid malignant cancers and about 1% of adults' (Jo and Fletcher, 2014). Epithelioid sarcoma (STeS) is one slow-growing histotype of STS, often found under the skin of fingers, hands arms or legs. The microbiota, which is the community of microorganisms leaving in symbiosis with our body, can be found on every surface associated to the external world, including the skin. The microbiota plays a major role in participating to tumor development and progression (Sears and Garrett, 2014) but it can also predict the response to therapy in melanoma, lung and renal cell carcinoma (Gopalakrishnan et al., 2017; Gopalakrishnan et al., 2018; Pitt et al., 2016; Routy et al., 2017; Vanpouille-Box et al., 2017; Viaud et al., 2015; Zitvogel et al., 2016; Zitvogel et al., 2017). Most of the activities of the microbiota are mediated by their metabolic output, i.e. the metabolites produced during their growth. These metabolites together with those produced by the tumor, the metabolome, may also participate to tumor growth and progression. The role of the microbiota in STS and in particular in epithelioid sarcoma is unknown. Many tumors have been described to harbour an intratumoral microbiota (Nejman et al., 2020), and we found that the intratumoral microbiota plays a major role in tumor metastasis process(Bertocchi et al., 2021). Given the peculiar location of epithelioid sarcoma, it will be interesting to evaluate the intertumoral microbiota and whether it may participate to the aggressiveness of this histotype.

Preliminary data

We have started to analyse both the metabolome and microbiota of STS. We found that the metabolome of the tumor is very different from that of the adjacent healthy tissue. In particular, it is more similar the metabolome of the tumor of different histotypes than that of the healthy tissue suggesting that the metabolic output of the tumor and the microbiota may be common across different histotypes and may charac terize STS as a whole. In addition, we observed that STS independent on the histotype is characterized by the presence of an intratumoral microbiota suggesting that the latter may play a role in tumor development and progression. In addition, we have received one sample of STeS and found that it was full of bacteria. Given the location of the tumor (under the skin) we still do not know whether these bacteria may be contaminating bacteria coming from the overlying skin or be specific to the STeS.

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Proposed project

In this project we will evaluate the role of the microbiota in STS progression. We have isolated many strains from STS, including STeS, and we will evaluate whether they can render the tumor more aggressive. We have two aims of the project:

1. Characterize the intratumoral microbiota of STS.

In this aim we will sequence the genome of the isolated bacteria both from STS and STeS and identify their nature. This will allow us to evaluate whether there are strains which are characteristic of STeS, versus other STS, and whether they are contaminating from the overlying skin.

2. Evaluate the effect of isolated bacterial strains on tumor cell metabolism and migration

Incubate different STS cell lines already available in the laboratory with the isolates mentioned above and evaluate what is the effect on tumor cell metabolism and migration. These experiments will be performed in vitro using sea horse for tumor cell metabolism and transwell systems for the migration.

Altogether these experiments will shed light on the role of the microbiota in tumor cell function and migration and will be correlated with the prognosis of the subject from which we have isolated the different bacterial species.

Budget

Requested funding 10.000 Euros including bacterial strain genome sequencing, purchase of materials and reagents for metabolomic analysis, antibodies, plasticware, enzymes, cell culture media. Dedicated personnel.

Time for execution: 1 year

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