**PROGETTO DI RICERCA**

**Targeting the intratumoral microbiota to reverse therapeutic resistance in bone metastasis from prostate cancers.**

*(Il microbiota intratumorale come bersaglio terapeutico per contrastare la resistenza alle attuali terapie per il trattamento delle metastasi ossee dei tumori della prostata)*

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*Premessa:* L’attività di ricerca sarà svolta presso l’Istituto Ortopedico Rizzoli IRCCS (IOR, Bologna) e nell’ambito del progetto “Targeting the intratumoral microbiota to reverse therapeutic resistance in lethal prostate cancers” PRIN 2022.

**Descrizione breve attività di ricerca**

Il progetto prevede l'arruolamento di pazienti con metastasi ossee da carcinoma prostatico, l'analisi del microbioma tumorale nelle metastasi e la valutazione del suo ruolo nella progressione del tumore e nella resistenza ai farmaci, attraverso studi sul microbioma stesso e modelli sperimentali in vitro. I dati ottenuti sulle metastasi ossee verranno integrati con quelli di altre sedi metastatiche per avere un quadro completo.

*The project involves enrolling patients with bone metastases from prostate cancer, analyzing the tumor microbiome in the metastases, and evaluating its role in tumor progression and drug resistance through studies on the microbiome itself and experimental in vitro models. The data obtained on bone metastases will be integrated with those from other metastatic sites in order to have a complete picture.*

**Introduzione**

Il cancro alla prostata (PC) è una delle principali cause di mortalità per tumore negli uomini nonostante gli importanti progressi terapeutici (1). Lo sviluppo di terapie per il PC si è concentrato sul targeting dei meccanismi cellulari intrinseci della segnalazione oncogenica. Tuttavia, fattori esogeni come dieta e obesità influenzano anche la cancerogenesi prostatica e la crescita del PC alterando infiammazione e metabolismo. Vi sono anche crescenti evidenze che il microbioma gastrointestinale (GI) possa similmente impattare l'insorgenza e la progressione del PC (2,3). La disbiosi, o squilibrio microbico GI, è implicata nella cancerogenesi, nella tollerabilità dei farmaci antitumorali e nell'efficacia. Sono state riportate differenze nel microbiota GI in pazienti con e senza PC (4-6). Tuttavia, i meccanismi attraverso cui i microbi impattano la cancerogenesi prostatica e la crescita del PC all'interno del microambiente tumorale, soprattutto a livello delle metastasi ossee, rimangono del tutto non esplorati. Recentemente è stato dimostrato che i batteri GI sintetizzano steroidi androgenici, minimizzando l'efficacia della terapia (3,7). Tuttavia, se il microbiota contribuisca alla cancerogenesi prostatica e alla resistenza al trattamento a livello tumorale rimane sconosciuto.

**Obiettivo dello studio**

In questo progetto si intende comprendere in che modo il microbiota umano contribuisca alla crescita del PC nell’osso, alla resistenza al trattamento. I risultati di questa proposta saranno di diretta rilevanza terapeutica poiché l'elucidazione meccanicistica dell'interazione tra microbi ospiti e tumori prostatici, a livello metastatico, faciliterà la progettazione di interventi per migliorare l'esito del PC.

Gli obiettivi specifici del progetto sono:

1) Arruolare pazienti con metastasi ossee da carcinoma prostatico e raccogliere campioni biologici.

2) Analizzare il microbioma tumorale nelle metastasi ossee di pazienti con carcinoma prostatico avanzato.

3) Studiare in vitro, utilizzando modelli di colture cellulari 3D, il ruolo del microbioma nella progressione tumorale e nella resistenza ai farmaci delle metastasi ossee da carcinoma prostatico.

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**PIANO DELLE ATTIVITA’**

###### Laboratorio dove saranno eseguite le prove

L'attività dell’assegnista di ricerca sarà svolta presso l’Istituto Ortopedico Rizzoli IRCCS (IOR Bologna), presso la SC di Scienze e Tecnologie Biomediche e Nanobiotecnologie (Responsabile Nicola Baldini).

**Materiale e Metodo**

L’assegnista di ricerca si occuperà di:

* Raccolta biopsie metastasi ossee da pazienti con carcinoma prostatico.
* Fissazione tessuto in formalina e paraffina, o congelamento in azoto liquido. Taglio delle sezioni in paraffina.
* Estrazione DNA per l’amplificazione 16S rRNA con tecniche NGS.
* Creazione di un modello microfluidico 3D con idrogel e cellule ossee e tumorali.
* Isolamento di ceppi batterici dal microbioma e generazione di supernatanti.
* Test dell'effetto dei supernatanti su vitalità e metabolismo delle cellule tumorali.
* Valutazione effetti dei supernatanti sulla chemioresistenza a farmaci antitumorali.

**Piano di formazione dell’assegnista**

La formazione del titolare dell’assegno sarà integrata da:

1) Formazione sulla conduzione di studi clinici;

2) Formazione sul microbiota tumorale;

3) Formazione sull’esecuzione di saggi di vitalità cellulare;

4) Formazione su colture cellulari 3D in dispositivi di microfluidica;

5) Analisi statistica dei dati, con uso di tecniche uni- e multivariate.

Al termine del periodo di ricerca, il titolare avrà acquisito competenze di alto livello sullo studio del microbiota tumorale e sullo sviluppo di modelli tumorali tridimensionali.

*Partecipazione a seminari e corsi*

* Meeting interni di laboratorio e Journal Clubs;
* Eventuali seminari ed eventi scientifici nazionali ed internazionali.