A multiplexed Enzymatic Repair Assay stratifies head and neck cancers and patients treated by chemo-radiotherapy

INTRODUCTION

Radiotherapy and chemotherapy induce a wide variety of lesions to the DNA. Healthy tissues and tumor cells have the ability to sense this variety of lesions and elicit a coordinated response with an impact on treatment efficacy (resistant tumors) and treatment-induced toxicity. Both the abilities of treatments to induce several lesions into the DNA and of cells to repair these lesions influence tumors resistance and patients sensitivity.

Defining sub-group of patients according to their sensitivity/resistance is one of the main developments for increasing therapeutic effects.

THE CHEMRAID CLINICAL TRIAL

Starting from blood samples of patients afflicted with Head and Neck Cancers

Starting from tumor biopsies of patients afflicted with Head and Neck Cancers

STEP 1: SAMPLES COLLECTION

Blood samples and tumor biopsies of patients afflicted with head and neck cancers were collected before and in the time course of the neo- and/or radiotherapy treatment.

Day 0: Before the treatment
Day 2: Two days after the treatment
Day 6: Six days after the treatment
Day 21: Twenty-one days after the treatment

STEP 2: PROTEINS EXTRACTION

The nuclear and whole cell extracts were prepared from Peripheral Blood Mononuclear Cells (PBMCs) and tumor biopsies and contain all DNA repair enzymes.

STEP 3: FUNCTIONAL ANALYSIS

Multiplexed biopsies are functionalized with a panel of specific DNA lesions which are repaired by the enzymes present in the cells extract.

DNA lesions on the biotin
Enzymes-
Repair
Enzymes
DNA Damage Response
DNA Repair

Each sample is characterized by a highly specific DNA Repair Signature

RESULTS

The preliminary results of this approach show an inter-individual variability in DNA repair capacities at basal level and treatment-induced in both PBMCs and tumor cells.

A high inter-individual variability in repair mechanisms of 6 specific lesions is shown before the treatment starts (Day 0). After two or five days of treatment, an induction of oxidized bases and abasic sites repair mechanisms was observed.

The scatter graph represents the correlation between different repair pathways induced before and after treatment in 22 patients. The induction of repair mechanisms is heterogeneous highlighting some significant outliers that could suggest the apparition of treatment-induced adverse effects.

PERSPECTIVES

We want to correlate these experimental data with the clinical data at the end of the study in order to:

• Identify patients at risk of adverse effects
• Classify tumors based on their real DNA repair capacities
• Refine mutation-based classification to define personalized treatments