Imaging of tumor specific antigens and microenvironment

Galli, Filippo

Chapter 7

Conclusions and future perspectives

Given the high degree of dedifferentiation and heterogeneity that may be encountered in cancer, in recent years the therapeutic and diagnostic approaches in clinical practice are slowly changing to a molecular level. This is because of the need to fully characterize each disease and to plan the best available therapy for each situation. From this point nuclear medicine techniques may greatly contribute to develop novel radioparmaceuticals virtually against any kind of available marker. Therefore, researchers are focusing on radiolabelling many peptides, hormones or mAbs to find the most suitable for their purpose. For example, in the field of thyroid cancer the need of a diagnostic and therapeutic tool to both image and treat non-iodine uptaking metastases is an open challenge since years. Many radiopharmaceuticals have been and are being studied over the years but, till now, none of them proved a great superiority and ^{131}I ^{18}F-FDG are still the most used for DTC and PDTC diagnosis and follow up. Indeed, given the high degree of dedifferentiation and heterogeneity of thyroid cancer, it is not easy to find specific ubiquitary markers present in DTC, PDTC and ATC. In the present thesis we proposed a completely novel approach to image non-iodine uptaking metastases focusing not only on the cancer cell itself, but also on the components that contribute to the formation of the microenvironment.

Superagonist rhTSH analogues, TNFα, anti-CD56 mAb and $VEGF_{165}$ were selected against four different targets present on tumor cells or the microenvironment. These molecules were radiolabelled with the same validated procedure, using ^{99m}Tc as the isotope of choice. The bifunctional chelator HYNIC

was used to indirectly radiolabel each compound using tricine as a coligand and $SnCl_2$ as reducing agent. This methodology was minimally invasive and the molecular structure was retained as confirmed by in vitro quality controls. QC included ITLC and HPLC analysis with different stationary and mobile phases, SDS-PAGE electrophoresis and HYNIC quantification experiments. In vitro binding assays on cells expressing the targets of the four radiopharmaceuticals were performed to prove that also their biological activity was retained with high affinity and specificity. Such experiments were important to plan animal studies were we could visualize tumor xenograft from DTC, PDTC and ATC derived cell lines.

Our approach may change the management of patients affected by cancer.

On the basis of the degree of differentiation and tumor type we can select the most appriopriate radiopharmaceutical to image metastases or exploiting microenviromental targets. Additionally, such tools, could allow to select patients for the most appropriate targeted therapy, that may range from immunotherapy to antiangiogenetic therapies using anti-VEGF mAb or TKI blocking the VEGFR signalling. This will save money and time allowing to select patients and predict the outcome of the therapy.

The possibility to image pro-inflammatory factors in vivo, with the ultimate goal of image cancer-related inflammation, was also explored in granulomas, which are benign tumors composed by inflammatory cells. Since the presence of TNF was not significantly reported in analysed lesions, it could be possible to conclude that

the studied patients, would not have benefit from anti-TNF targeted therapy. This is a practical example of in vivo characterization of lesions and therapy decision-making.

In the future we would like to follow this very same approach and extend it to many cancer types, to develop new tools and strategies against as many marker as possible, in order to increase our arsenal against cancer.

Finally, in the future it will be possible to radiolabel such radiopharmaceuticals with positron emitting isotopes to take advantage of PET resolution and quantification. On the other hand, tumor specific radiopharmaceutials like TR1401 could be radiolabelled with beta-emitting isotopes. This will allow diagnosing and treating lesions with the same pharmaceutical as proved by the introduction of theranostics like DOTA-TOC and DOTA-NOC.