Opinion

Early detection of melanoma with synchrotron radiation X-ray fiber diffraction analysis

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Skin is the largest organ in our body protecting us from ultraviolet radiation and xenobiotics. The function of keratinocytes is to form the impermeable barrier for the skin and rest of the body, whereas melanocytes provide the pigment for the keratinizing skin layers to protect the integrity of keratinocytes, basal cells, immune cells and many other dermo-epidermal structures. Pigmented nevi are considered to be precursor lesions for malignant melanoma of the skin. They harbor genetic alterations such as oncogene BRAF. However, although nevi can give rise to melanoma, not all pigmented lesions become malignant as nevi are usually senescent and permanently growth arrested; only a fraction of melanomas arises from the existing nevi. When atypical pigment cells show invasive and proliferative behavior, melanoma pathogenesis has progressed. Melanoma cells have become independent from keratinocyte control, cell-cell interactions are altered and motility program is activated. Mutations in melanoma are manifold including driver type oncogene mutations such as BRAFV600E- mutation in the MAPK-signaling, leading to the activation of this pathway, or inactivating tumor suppressor genes.

Norway has the highest incidence of melanoma in Europe, 16 per 100000 person years [1]. Melanoma diagnosis is histological and therefore requires a surgical biopsy with further resections if necessary, always following a pathologist's report. The prognosis can vary and is heavily dependent on the thickness of the melanoma lesion. Thickness defines the tumor class in the TNM staging and is measured in millimeters according to Breslow or in skin according to Clark's classes. If it is surgically removed in its early stages as a thin lesion, the patient can be

cured from melanoma. For advanced and metastatic melanoma, new targeted and immunological treatments are available improving the survival of melanoma patients dramatically, in addition to the old and relatively inefficient dacarbazine. The tumor microenvironment populating cells consists of carcinoma-associated macrophages (CAMs), carcinoma-associated fibroblasts (CAFs), endothelial precursor cells and pericytes [2]. In addition, lymphocytes, from the adaptive immune system, are an important part of the tumor landscape. Tumor infiltrating lymphocytes (TIL's) in primary lesions offers a practical tool in the assessment of melanoma prognosis [3]. Checkpoint inhibitors have emerged as promising drugs to treat metastatic melanoma. Nivolumab is PD-L1 antibodies that interrupt the receptor-ligand binding of lymphocytes and melanoma cells, ultimately leading to cancer immune response.

In the treatment of skin diseases, skin is easily accessible, and topical treatment options have a lot of potentials. Even if surgery is the treatment of choice for neoplastic pigment cell lesions, there are situations where topical approaches would be more suitable. In addition, altering the inflammatory landscape of psoriasis or a cancer would be a means to treat these skin diseases. A synchrotron facility could through imaging techniques contribute to a more detailed understanding of the origin and the manifestation of disease. Imaging techniques could aid detection and analysis of single cells that are more representative of the skin cancers developed by most patients, as well as non-uniform cancer cells, regardless of their origin. Synchrotron radiation has major advantages of high resolution, increased flux and brilliance, and the choice of specific photon energy for the experiment.

Rosalind Franklin used the X-ray fibre diffraction method in discovery structural information of DNA and Veronica J. James is using the same technique to provide an accurate diagnosis of cancers including breast cancer, prostate cancer and melanoma and answer to the question, 'Is my cancer cured?' [4-6,8-9]. X-ray diffraction is sending x-ray particles through biological samples, as they go through and some of those particles are deflected by the underlying molecular structures of their substances. For example, the X-ray diffraction of hair, most of the particles go straight through and a few particles are deflected by the alpha-keratin that makes up the hair fiber. They end up interfering with each other and causing a distinctive diffraction pattern and observe images with a circle in the middle and a whole lot of arcs around it. The arcs reflect the spacing of the molecular structures of the hair. Using synchrotron radiation, Veronica J. James show that some

patients have an additional feature in the diffraction pattern, which is a circle and that appear in the hair from a patient who had breast cancer [4, 5, 10]. The diffraction patterns changes are introduced by the presence of the cancer cells in the body. By using skin tissue, the diffraction patterns only of the dermal collagen can be obtained. The changes noted in the diffraction pattern for melanoma patients had a single additional ring with spacing of 4.03 nm in the same location [6]. Those findings show that, it's possible to detect melanoma in the patient's skin sample long before they developed the disease.

Synchrotron X-ray fibre diffraction analysis, could lead to better and faster diagnoses for the life-threatening disease, which is a key in preclinical research. This is a unique tool which offers not only a powerful early diagnostic method for patients, as well a fascinating research field. Fibre diffraction could replace the very costly blood tests presently in use for this gene test [10]. Up to now, the biological mechanism to explain the changes in the diffraction patterns was unknown but the result is consistent and specific to the type of cancer. Recently work, emphasis the hypothesis that cathepsins is released systemically by tumors before is clinically observed and leave the molecular 'signature' in alpha-keratin and collagen [7]. As the authors suggested, call for more research with the synchrotron radiation X-ray fiber diffraction analysis is needed, in order to understand the efficiency of cathepsins in the early diagnosis and treatment of cancers. Therefore, we do need to conduct more research with a sensitivity of 100% and a specificity of 99.1% in over 4500 patient samples for cancer diagnosis should be sufficient to prove this technique works [11]. Suitable beam-lines are necessary to investigate high volume of patient sample. The synchrotron X-ray fiber diffraction analysis of hair and skin is a reliable, sensitive and cost-effective method as well a fantastic tool for cancer diagnostic and treatment.

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