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Determination of collagen ultrastructure in cancer tissue via unsupervised ML analysis of P-SHG image parameters

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Polarization-resolved Second Harmonic Generation (P-SHG) microscopy is a non-linear imaging technique that enables label-free, non-destructive imaging of fibrillar collagen distribution and allows determination of collagen fibers orientation and ultrastructure. Papillary thyroid carcinoma (PTC) is the most common endocrine tumor and accounts for over 80% of thyroid cancers [1]. PTC nodules are often surrounded by a capsule consisting predominantly of fibrillar collagen, which can undergo significant structural changes as the disease progresses. Early detection of these changes is crucial as most thyroid cancers are treatable if diagnosed early.

In the present study, we analyzed the ultrastructure of collagen fibers in the PTC capsule in terms of the collagen triple helix pitch angle (θ) using a uniaxial molecule model [2] in the approximation of cylindrical symmetry. Nonzero elements of the macroscopic nonlinear susceptibility tensor for the model were extracted from P-SHG images accumulated with a custom-built wide-field P-SHG setup [3]. All the obtained parameters were subsequently used for unsupervised machine learning (ML) model and clustering of PTC nodule sections was performed.

We found that the spatial distribution of collagen fibers and their ultrastructure in the invaded regions of the PTC capsule differed from those of the non-invaded areas. The invaded areas were dominated by collagen fibers composed of close-packed triple helixes with an average pitch angle of 43.9°, whereas the intact capsule was characterized by collagen fibers with a θ of 42.5°. In addition, the proportion of fibers with a θ of 37.9° was significantly reduced in the invaded areas compared to the areas without invasion. Such differences in the ultrastructure of fibers have been shown to affect the efficiency of collagen binding to the cells, facilitating the spread of cancer cells along the fibers [4] and thus contributing to metastasis.

Visual inspection of cluster maps of PTC capsules enables rapid detection of pathological changes in the ultrastructure of collagen fibers. The proposed approach based on ML analysis shows strong potential for early diagnosis of PTC capsule invasion [5].

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