Macrophage subgroups distinguish knee osteoarthritis patients; innovative technology can now reveal their spatial localisation within the joint

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Background

Osteoarthritis (OA) is a debilitating disease and the most common form of arthritis. Inflammation has been found to contribute to pathogenesis, however inadequate understanding of cellular and molecular mechanisms has meant that anti-inflammatory therapeutics have largely been unsuccessful. Recent findings pinpoint a role for synovial macrophages, identifying that OA patients can be grouped based on the presence of inflammatory-like (iOA) macrophages showing a clear proliferation signature, or classical-like (cOA) macrophages characterised by tissue-remodelling features. This highlights the heterogeneity of OA. A better understanding of the joint immune landscape could reveal novel therapeutic targets and/or lead to the development of new tools to stratify patients for disease-modifying treatments based on macrophage phenotypes.

Methods

An optimised tissue digestion protocol and fluorescence-activated cell sorting were used to purify synovial tissue immune cell subsets. RNA-sequencing was performed on synovial tissue macrophages revealing heterogenous phenotypes. Synovial tissue sections were stained with a panel of metal-tagged antibodies to identify synovial macrophage subsets and other immune/non-immune populations. Using Hyperion Imaging Mass Cytometry, regions of interest were ablated, and metal-tagged antibody location identified by time-of-flight measurements. Reconstructed tissue images were created and populations identified using phenograph clustering. Populations were mapped back to the tissue image to identify cellular spatial localisation.

Results

Computational analysis of flow cytometry data sets demonstrated an increased proportion and activated phenotype of macrophages in OA synovial tissue. Two distinctive OA endotypes were proposed based on their functional gene signatures, comprised of cell proliferation mechanisms, or tissue-remodelling features. Hyperion technology was capable of identifying the spatial localisation of macrophage subsets within OA synovial tissue samples without losing in-depth phenotypic information. Importantly, $Ki67^+$ iOA macrophages could be identified. Data thus far indicates this subgroup is located primarily at the intima lining layer of the synovium rather than in close proximity to immune cell aggregates.

Conclusions

Hyperion Imaging Mass Cytometry can assess the synovial immune landscape. We have used this technology to detect the cellular locations and interactions of iOA and cOA macrophage subsets identified as the defining characteristics of two pathologically distinct forms of OA. We can now uncover the cellular interactions that underlie these different pathological processes, and potentially generate new treatments for this intractable disorder.