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Short Communication

Targeting cancer-associated fibroblasts - Are we there yet?

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1. Background

Cancer biology studies indicate the intricate interplay between several cells in the tumor microenvironment (TME) other than the tumor cells themselves. Intratumoral heterogeneity is a well described entity which makes cancer a dynamic disease and, more significantly, it has several implications in therapeutic interventions.[1]

2. What are Cancer Associated Fibroblasts?

CAFs are a group of activated fibroblasts with significant plasticity and are a major player in contributing to tumor heterogeneity which have diverse functions. CAFs are spindle-shaped cells that build up and remodel the extracellular matrix structure.[2] They are characterized by increased expression of markers such as alpha smooth muscle actin (α-SMA), fibroblast activation protein (FAP), fibroblast-specific protein 1 (FSP1), platelet-derived growth factor receptor (PDGFR)-α/β and vimentin.

Fibroblasts in the TME are exposed to cytokines and other growth factors like TGF-β, PDGF, FGF2, HGF, IL-1 and IL-6, which reprogram the phenotype of these cells. Although most of the studies quote CAF's performing tumor promoting functions, some evidence indicates that they have tumor suppressive functions especially in early stages (cancer-restraining CAFs).[1,3]

Development of new co-culture models and the implementation of single-cell RNA-sequencing (scRNA-seq) techniques have revealed a high level of heterogeneity in CAF functions. For example, in pancreatic cancer CAFs expressing α SMA accelerated tumour growth while CAFs expressing FAP resulted in an impairment of tumour growth. This in itself indicates the complexity of CAF biology.[4]

CAFs have been classified into various subtypes - Inflammatory CAFs, Myofibroblastic CAFs, Antigen Presenting CAFs. The cell of origin (COO) of CAFs in different tissues have been put forward like mesenchymal stem cells, pancreatic and hepatic stellate cells etc. but a definite evidence is lacking. CAF subtype-specific lineage tracing models coupled with in vivo imaging methods could throw more light.[5]

3. Implications of CAFs in Cancer Therapy

A large number of studies have shown that CAFs promote resistance to therapy due to their interplay with cancer stem cells (CSCs). The mechanisms include promotion of expansion of a subset of cancer cells with stem-like properties, activation of alternative signaling mechanisms and secretion of extracellular matrix which can form a physical barrier for entry of chemotherapy. CAFs can also modify the immunologic nature of the TME thereby preventing immunologic cell death.[4] Cancer therapy by itself can lead to a pathway of resistance via secretion of various chemokines and cytokines during cell senescence

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and by activation of alternate signaling pathways.[5] This is sometimes referred to as activation of inflammatory gene signature by chemotherapy.

4. Targeting CAFs - Where are we now?

There have been several ways which have been attempted for targeting CAFs. Regardless of the method, the main aim is to normalise the tumour-stroma interactions and ensure that the crosstalk between fibroblasts and tumor and immune cells do not cause therapeutic failure.

Low dose Metronomic therapy is a method of overcoming this problem because high doses of chemotherapy promote the release of proinflammatory mediators, activate alternate signalling pathways by CAFs and cause tumor stromal changes; all of which lead to therapy resistance. There have been several clinical trials which have supported the use of low dose metronomic therapy in advanced cancers that have led to good and long term cancer control without deterioration of quality of life.[6]

Another novel method upcoming in oncology is drug repurposing. This means that drugs which are approved for other indications may be used for cancer therapy. The rationale for its use is that it targets the alternate pathways which are activated during cancer therapy. There are also indications that some of these drugs directly target the cells in TME. Moreover, the use of repurposed drugs is considerably more accessible and affordable. For example, metformin has been tried in combinatorial therapy for cancer treatment and shown positive results.[7] Several other drugs under antihypertensives like propranolol, anti hyperlipidemic drugs like rosuvastatin ,antihelminthic drug, Mebendazole ,have mirrored similar results.

Direct attacking of CAFs using Chimeric Antigen Receptor (CAR) T cell therapy and cancer vaccines (dendritic cell vaccines) are in preclinical studies. Near infrared photoimmunotherapy and miRNA based targeting of CAFs are innovative approaches for depletion of CAFs from tumor stroma thereby reducing chances of cancer resistance and progression. Unique antibody drug conjugates are also being developed to target CAFs in the TME as a second hit to chemotherapy.[4]

5. Future Directions and Conclusions

Overall, the future looks bright for CAFs as a potential target for cancer therapy. Newer avenues like phenotypic switching of tumor promoting CAFs to cancer restraining CAFs, targeted ablation of tumor promoting CAFs with specific and convenient biomarkers, epigenetic programming for reverse modulation of stromal cells etc are exciting novel strategies in the pipeline. The problem of cancer therapy resistance is plentiful, especially with the advent of newer modalities of therapy resulting in improved survival among patients.

Cancers are becoming very ‘clever’ trying to evade whatever we throw at them. One of the major ways it does it is through changes in TME rather than the malignant cell itself. But with faster developments, we can overcome these hurdles. The need of the hour is to translate positive results of preclinical studies to clinical benefits with innovative clinical trial methodology.

6. Source of Funding

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7. Conflict of Interest

None.

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