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The Cancer Immunotherapy Armamentarium: Assessing Applications, Ambitions, and Amplitude

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Introduction

- Cancer is the second leading cause of death worldwide with a 70% increase in cases is expected over the next 20 years.1
- Immunotherapy was recognized as advancement of the year in both 2016 and 2017.2
- Positive initial findings and clinical results of recent immunotherapies has precipitated a wave of attention and interest into the field, both in the general public and within the biomedical community.
- Some experts have speculated that this influx of attention and focus on immunotherapies has gone too far.3
- Others within the field think all the attention and support focused on immunotherapy can only be a good thing, and cultivates a landscape in which inquisition and competition leads to the best answers.4
- The aspect agreed upon by both sides: more funding and support of cancer research is needed.
- The importance of allocating funds and support sensibly is then critical.
- To achieve this, it is imperative that research areas and therapeutic modalities are assessed for current and prospective functionality, applicability, and amplitude.

Background

- Etiology, progression, and prognosis varies from one cancer type to another; the commonality is the abnormal proliferation of cells leading to malignant neoplasia (Fig. 1).
- A hallmark of cancers is their ability to suppress and/or evade the anti-tumor defenses of the immune system.3
- Restoration and enhancement of immune function within the neoplastic microenvironment is thereby a logical and promising path to continue pursuing in the fight against cancer.

Current Approaches

Checkpoint Inhibitors
- Two common targets: PD-L1 and CTLA4
- Only approved for treating 10 of over 100 cancer types5
- Side effects: complications; autoimmune hepatitis, pneumonitis, pulmonary toxicity5
- Overtreatment in clinical trials: currently over 1100 active trials5

Anticancer vaccines
- Anticancer vaccines use tumor antigen information, delivered via dendritic cell, peptide, or genetic vaccine to activate the patient’s immune system to fight cancer7
- Relatively safe, lower incidence of side effects7
- Problems: low affinity, response maintenance, mismatching, degradation, insertional mutagenesis7

Adoptive Cell Transfer (ACT)
- Tumor infiltrating lymphocyte (TIL), T cell receptor (TCR), and chimeric antigen receptor (CAR) are three most common ACT therapies. (Fig. 5)
- In TIL, lymphocytes are harvested from patient, the most effective are isolated, stimulated for growth to achieve therapeutic numbers, and then reinfused.6
- In TCR and CAR, T cells are harvested from the patient, engineered to highly express either a ligand binding receptor or chimeric antigen receptor, expanded, and reintroduced to the patient.10
- Challenges/limitations: immune-depletion of already ill patients from cell harvesting, lack of persistence, antigen escape, and are difficult to produce with efficiency.6

Potential adverse effects: hyperimmune response triggered toxicity including cytokine release syndrome, renal failure, neurotoxicity, and other on-target but off-tumor toxicity.11

Future Directions

Nanocarriers
- Nano carriers (NGs) have the potential to be a targeted delivery system for cancer therapies.
- Can be targeted passively, or for specific proteins or pH levels.
- New form is coated with specific cancer cell proteins chosen for their physiological effects.11

Mechanogenetics
- Mechanogenetics involves bioengineering cells that directly affect the transcriptional activity of target cells and can be activated remotely within a confined tissue space such in/around a tumor.12
- Advantages of mechanogenetics are its non-invasiveness and reversibility.
- Control genetic activity via chemical, radio, magnetic wave, or ultrasound activation of elements coupled with cellular channels which ultimately propagate nuclear signaling pathways.12

Epigenetic modulation
- Many of the mechanisms by which cancer evades the immune response are epigenetically regulated.
- These are like tags added to DNA that can affect how much of areas are available for transcription.
- This tagging/un tagging is carried out by two specific protein enzyme families.
- Pre-clinical studies have shown inhibitors of these enzymes can both reverse the modifications as well as improve the anti-tumor immune response in models of some cancer types.13

Conclusion

- Immunotherapy is a promising field in cancer research and treatment, but could likely never be an all-encompassing savior in the fight against cancer.
- The challenge faced will be to work towards rational synergistic approaches with attainable applications and intelligent clinical designs.
- Interdisciplinary coordination and cooperation to appropriately allocate attention, funding, and further research will remain imperative to be most successful in elucidating and developing the best arsenal against cancer.

References

Figure 1. Normal cell division compared to cancerous proliferation.14

Figure 2. Cancer and the immune cycle. CC: cancer cell. DC: dendritic cell. TCC: cytotoxic T cell.18

Figure 3. Checkpoint inhibitors reinitiate the immune system by preventing the binding and inhibition by cancer cells at specific surface targets.14

Figure 4. Anticancer vaccine formats.9

Figure 5. Schematic of adoptive cell transfer based immunotherapies.4

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