Understanding Renal Cell Carcinoma and Immuno-Oncology Approaches

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Renal cell carcinoma epidemiology
Renal cell carcinoma (RCC) is the most common type of kidney cancer. About 70% of these patients have clear cell RCC and around 30% of patients present with advanced disease at the time of diagnosis. Renal cell carcinomas can mutate quickly and disease ultimately progresses. Currently, patients who have advanced disease are told that the disease is treatable, but not curable. Delivering a long-term survival benefit for patients with advanced renal cell carcinoma remains a goal.

Treatment modalities
The options traditionally available for most cancers have been chemotherapy, targeted therapy, radiation, and surgery, which are all intended to target the tumor, and potentially its microenvironment.

- **Chemotherapy** plays a limited role in treating advanced RCC.
- **Targeted therapy** can be used to treat advanced disease. Molecular targeted agents inhibiting the VEGF and mTOR pathways have been associated with downstream inhibition of cell growth, proliferation, metabolism, and angiogenesis.
- **Radiation** also plays a minor role in the treatment of advanced disease (except in the case of palliative treatment), since RCC is characterized as relatively radioresistant.
- **Surgery** is most commonly used to treat patients with localized disease, and may also be used in patients with advanced renal cell carcinoma if the lesions are resectable and patients have a good performance status.

The emerging modality of **immuno-oncology (I-O)** has the potential to enhance the body’s own immune system to defend against cancer cells. The goal of I-O is to **restore the ability of the immune system to**
Eliminate cancer cells by either activating the immune system directly or by inhibiting mechanisms of suppression by tumors.\textsuperscript{11-14}

RCC has been established as an immunogenic cancer.\textsuperscript{15} There is evidence specific to RCC that suggests potential for an antitumor immune response and susceptibility to immune attack in patients with this tumor type.

Steps in the normal immune system response to cancer:
1. Tumors express and release tumor-associated antigens; antigen-presenting cells (APCs) capture and process these antigens and present them to T cells.
2. Through costimulatory signals, T-cell activation is completed.\textsuperscript{19,20}
3. T cells are then able to proliferate and travel throughout the body. T cells proliferate by cloning themselves, creating more activated T cells which are able to recognize tumor cells.\textsuperscript{19,20}
4. Once T cells are activated, cytotoxic T cells migrate to the tumor, where they can recognize expressed tumor antigen and destroy tumor cells.\textsuperscript{19,20}
5. A subset of activated T cells becomes memory T cells to help generate a rapid cell-mediated immune response in the future.\textsuperscript{19,20}

Role of the immune system in renal cell carcinoma

The immune system has natural anti-tumor activity

Normally the innate and adaptive immune systems recognize tumor cells and initiate anti-tumor responses to eliminate cancer. This is known as tumor immune surveillance.\textsuperscript{16,17,18} However, in some cases tumor cells can manage to evade the body’s immune response.\textsuperscript{16}

Immuno-oncology is a novel treatment modality for advanced renal cancer
Renal cell carcinoma is an immunogenic cancer. There is the potential for an antitumor immune response and susceptibility to immune attack in patients with renal cell carcinoma (RCC). For example:

- **Diffuse infiltration of renal cell tumors with immune cells** has been observed. These immune cells include: T cells, dendritic cells, natural killer cells, macrophages, and memory cells.

- **Cytokines** also represent an interesting interaction between renal cancer and the immune system. Cytokines are molecular messengers that allow cells of the immune system to generate a coordinated response to a target antigen. A number of cytokines are also secreted by some tumors.

- **Tumor antigen-specific T cells** have been isolated in the peripheral blood of patients with RCC pointing to an anti-tumor response.
Mechanisms of tumor evasion

Tumor cells develop different strategies to escape immune recognition, which can lead to evasion of immune destruction and tumor growth.\textsuperscript{30} This ability to evade immune destruction is an emerging hallmark of cancer.\textsuperscript{31} Tumor evasion strategies can include:

- **Tumor antigens** – Renal cell tumors can alter or lose the expression of antigens, so that tumor cells are no longer recognized by cytotoxic T cells.

- **Immunosuppressive factors** – Renal cell carcinoma can promote the expression of immunosuppressive factors to ward off natural killer cells or cytotoxic T cells.\textsuperscript{32,33}

- **Immune checkpoint pathways** – Tumors can evade detection by altering the immune checkpoint pathways.\textsuperscript{34,35,36} Tumors can express ligands that are recognized by inhibitory receptors on effector T cells, such as CTLA-4, PD-1, and LAG-3. The binding of certain ligands to receptors can prevent T-cell activation.\textsuperscript{19,33,34}

- **Recruitment of immune cells** – Tumor cells can also inhibit the immune response through recruitment of regulatory T cells and myeloid-derived suppressor cells.\textsuperscript{37}
With the variety of mechanisms that tumors use to evade the immune system, a number of different modalities are being explored to activate an immune response against the tumor. In particular, the ability of tumors to evade immune recognition and destruction through manipulation of immune checkpoint and co-stimulatory pathways is currently being explored.

Understanding these immune pathways may provide insight into the mechanisms governing the interaction between renal cancer and host immune responses.

Tumors have evolved mechanisms to inactivate T cells by exploiting co-stimulatory and immune checkpoint pathways.
**Checkpoint pathways**

Under normal circumstances, immune checkpoint pathways are responsible for maintaining immune homeostasis. Immune checkpoint pathways such as CTLA-4, PD-1 and LAG-3 normally act to inhibit T-cell responses when no longer necessary.\(^9,34\)

**CTLA-4 is a checkpoint molecule expressed on activated T cells**.\(^{34,41}\) Left unchecked, activated T cells may react with and damage normal tissue.\(^{34}\) To limit this damage, T-cell activity is kept in check by the expression of the immune checkpoint molecule CTLA-4 on the surface of T cells. This limits the priming phase of T-cell responses within the lymph nodes.\(^{34,42,43}\) CD80/86 on the antigen-presenting cell is the ligand for CTLA-4. Binding of this receptor–ligand pair downregulates T-cell activity.\(^{34}\)

**PD-1 is another checkpoint molecule expressed on effector T cells** that acts as a negative regulator of immune response. Binding of PD-1 to its ligands, PD-L1 and PD-L2, inhibits T-cell activity.\(^{11,43}\)

Tumors, such as kidney cancer, frequently overexpress PD-L1 to defend against an immune response. When PD-L1 and PD-L2 are produced on the surface of the tumor, it effectively blocks the ability of T cells to attack cancer cells at the site of the tumor itself.\(^{30,34,44}\)
Expression of LAG-3 upon T-cell activation helps support feedback inhibition, similar to CTLA-4. The main ligand for LAG-3 is MHC class II molecules on APCs. Though its role is not completely understood, studies have shown that LAG-3 is associated with T-cell exhaustion (T cells with poor immune effector function).\textsuperscript{34,45}

In kidney cancer, LAG-3 has been shown to be expressed, potentially contributing to immune evasion.\textsuperscript{34,46}

PD-L1 and PD-L2 on renal carcinoma cells can bind to the PD receptor on T cells to inhibit T-cell activity and suppress the T-cell attack directly at the tumor site.

The immune checkpoint molecules, CTLA-4, LAG-3, and PD-1, are necessary for immune homeostasis. However, tumors are able to exploit these immune checkpoint pathways and suppress the immune system, which ultimately leads to tumor growth.\textsuperscript{34} Ongoing research seeks to understand if blocking the CTLA-4, LAG-3, and PD-1 pathways may augment T-cell activation and subsequent migration and attack of tumor cells.

As we improve our understanding of how tumors dysregulate co-stimulatory and immune checkpoint pathways, there is potential to inform future treatment strategies for renal cell cancers.\textsuperscript{34,35,36}
References