Understanding Renal Cell Carcinoma and Immuno-Oncology Approaches

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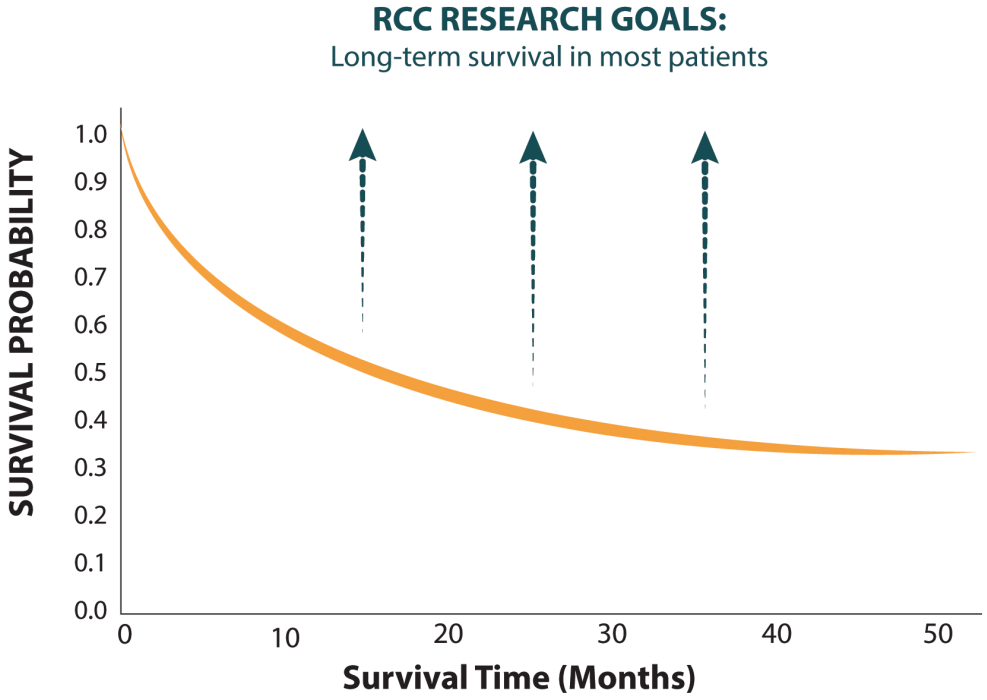
Introduction to Immuno-Oncology (I-O) in renal cell carcinoma

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.[1,2] 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.[1,3,4] Delivering a long-term survival benefit for patients with advanced renal cell carcinoma remains a goal.[1,5,6]



Treatment modalities

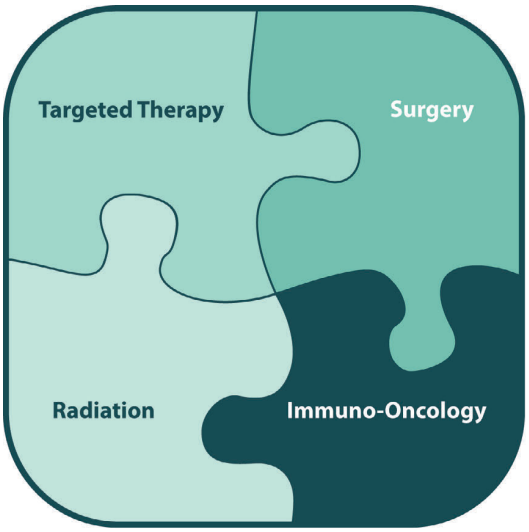
The options traditionally available for most cancers have been chemotherapy, targeted therapy, radiation, and surgery, which are all intended to target the tumor, and potentially its microenvironment.[1,7,8]

- **Chemotherapy** plays a limited role in treating advanced RCC.[1]
- **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.[1]
- **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.[1]
- **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.[1]

The emerging modality of **immuno-oncology (I-O)** has the potential to enhance the body's own immune system to defend against cancer cells.[9,10] 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.[11-14]

RCC has been established as an immunogenic cancer.[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.



Immuno-oncology is a novel treatment modality for advanced renal cancer

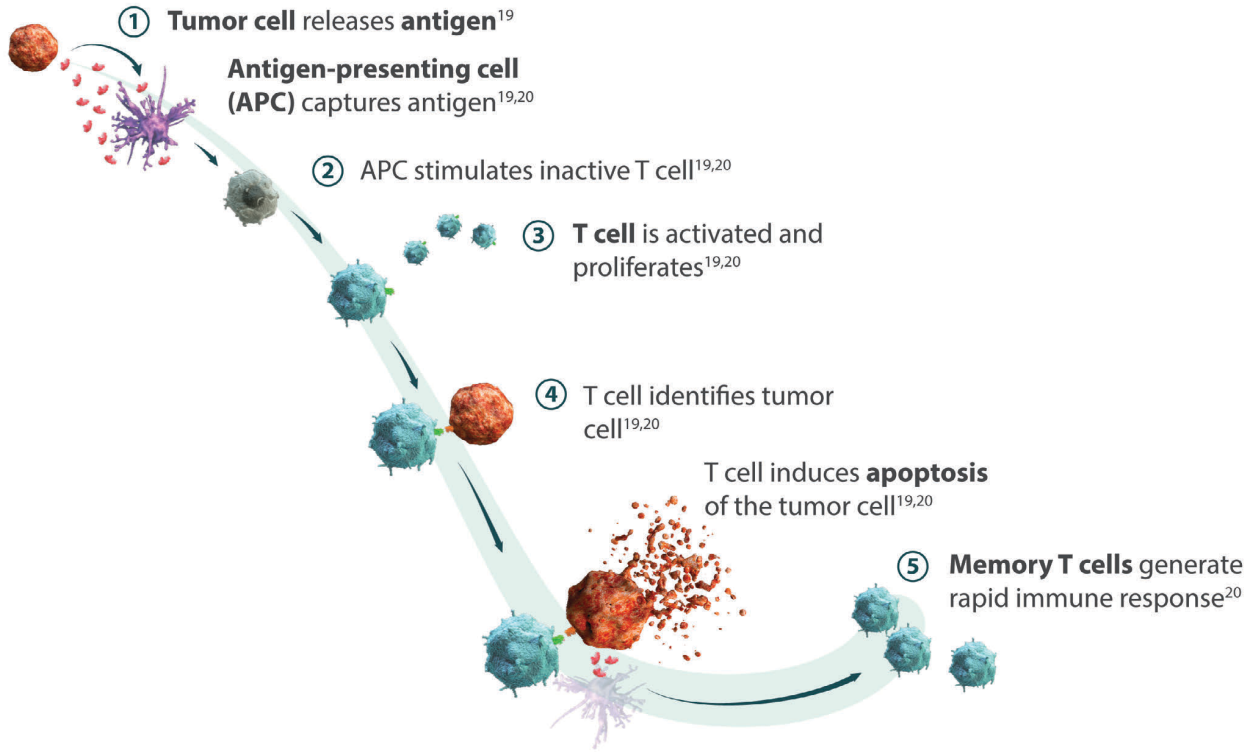
Role of the immune system in renal cell carcinoma

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.[16,17,18] However, in some cases tumor cells can manage to evade the body's immune response.[16]

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.[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.[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.[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.[19,20]



Pathway showing normal anti-tumor activity of the immune system

Renal cell carcinoma is an immunogenic cancer[15]

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.[5, 21-25]
- **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.[26,27]
- **Tumor antigen-specific T cells** have been isolated in the peripheral blood of patients with RCC pointing to an anti-tumor response.[28,29]

Tumor evasion of the immune system

Mechanisms of tumor evasion

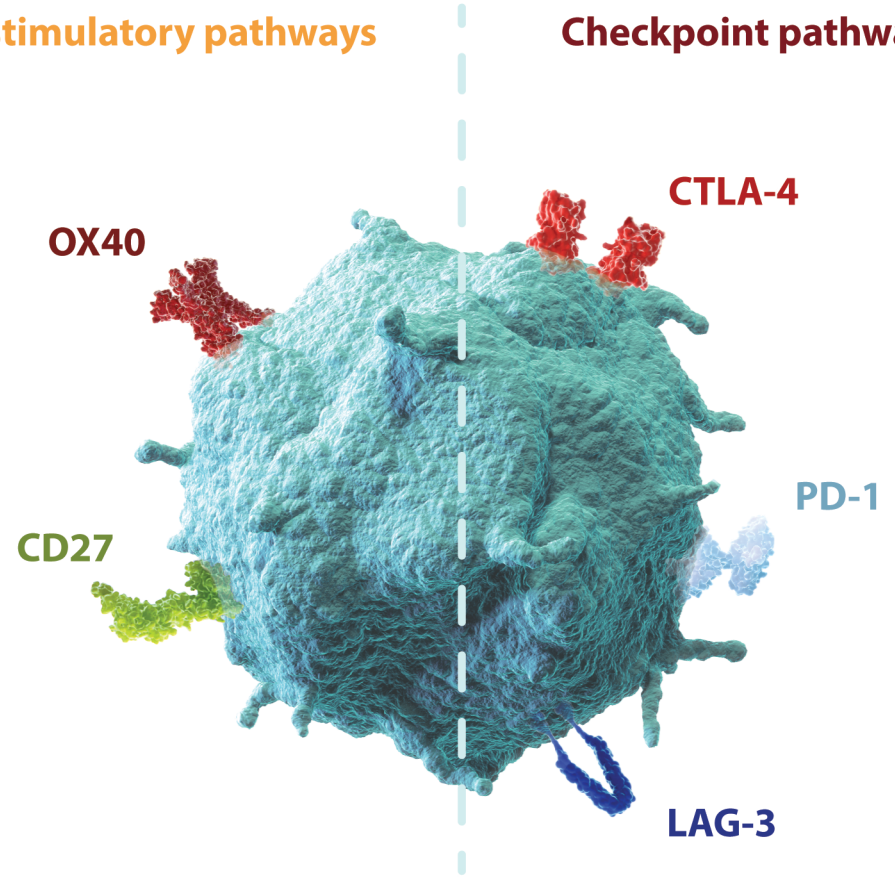
Tumor cells develop different strategies to escape immune recognition, which can lead to evasion of immune destruction and tumor growth.[30] This ability to evade immune destruction is an emerging hallmark of cancer.[31] Tumor evasion strategies can include:

- **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.[32,33]
- **Immune checkpoint pathways** – Tumors can evade detection by altering the immune checkpoint pathways.[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.[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.[37]

Immune system pathway mechanisms under investigation

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.[1,33-40] 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.[11]

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

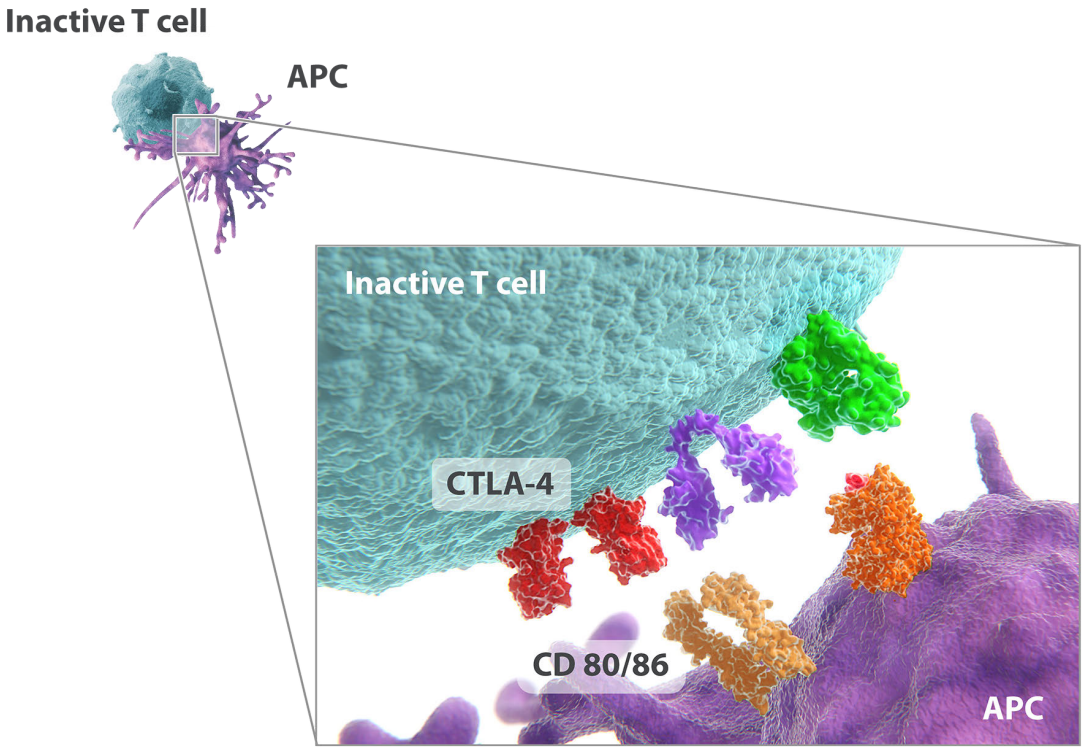


Tumors have evolved mechanisms to inactivate T cells by exploiting co-stimulatory and immune checkpoint pathways

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]

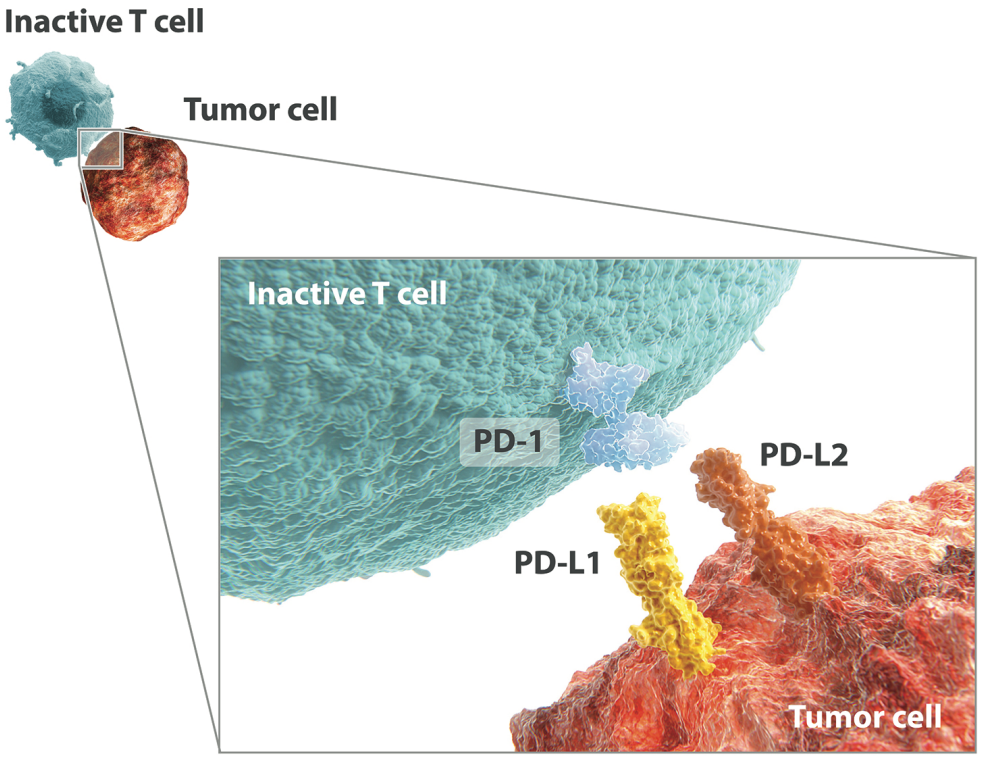
CTLA-4 is a checkpoint molecule expressed on activated T cells.[34,41] Left unchecked, activated T cells may react with and damage normal tissue.[34] To limit this damage, T-cell activity is kept in check by the expression of the immune checkpoint molecule CTLA-4 on the surface of T cells. This limits 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]



Interaction between the T-cell receptor CTLA-4 with its ligand CD80/86 on the APC downregulates T-cell activity

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]



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

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).[34,45]

- In kidney cancer, LAG-3 has been shown to be expressed, potentially contributing to immune evasion.[34,46]

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**.[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.[34,35,36]

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