**[TGF-β’s role in Immune Evasion of Colorectal Cancer and Anti-TGF-β Therapies]**

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**Colorectal cancer is a cancer that begins in the large intestine, or colon. When detected early, colorectal cancer will often begin as benign polyps in the colon that over time, turn malignant. These tumors begin in the mucosa of the colon and work out to the outermost layer of the subserosa and serosa. As of recent research, no mutations have been correlated with aggressive, metastatic cancer. However, the tumor microenvironment of aggressive subtypes of colorectal cancer has been discovered to have elevated TGF-β levels. Due to TGF-B’s role in promoting immunosuppression, angiogenesis, metastasis, and tumor cell epithelial-to-mesenchymal transitions (EMT)2, TGF-B serves as a theoretically good target for anti-cancer pharmaceuticals. However, preclinical studies in-vitro and in-vivo employing animal models are exhibiting drastically different results when compared to the current clinical study. This begs the question, are we overlooking key features of TGF-B in human models that lead to poor results in clinical trials? This question will be examined in this microreview.**

**Introduction**

The American Cancer Society estimates that there will be 104, 270 new cases of colon cancer in 2021 along with an estimated 52, 980 deaths during 2021. While no mutations have been correlated with metastatic colon cancer, increased TGF-B (transforming growth factor-beta) levels are a predictor of adverse clinical outcomes.

**Transforming Growth Factor-Beta**

In addition to what is stated above, TGF-B in cancer associated fibroblasts (CAFs) appear to shield the tumor microenvironment from immune infiltration. Data supports the idea that the mechanism of immune evasion through the promotion of T-cell exclusion and blocking of the TH1-effector cells is due to an increase in TGF-B in the tumor microenvironment(TME)3 and this is further aggravated by the presences of cancer associated. Furthermore, studies have indicated that cancer associated fibroblasts increase the frequency of tumor-initiating cells, which is “dramatically enhanced” by the presence of TGF-B signaling.1

**Epithelial-to-Mesenchymal Transition**

This cytokine, TGF-B, has been found to promote angiogenesis, metastasis, and tumor cell epithelial-to-mesenchymal transition (EMT)2. In metastasis, it is important for tumor cell epithelial-to-mesenchymal transition (EMT) to occur in order to increase their migratory potential. After the tumor reaches its secondary site, tumor cell mesenchymal transition to epithelial cells (MET) occurs to make the tumor favorable in its tumor microenvironment and improve its chance of proliferation. These are opposite multistep processes that allow metastasis to take place in the organism. TGF-B is a well-known inducer of the EMT effect on tumor cells1 and does so by controlling proteins related to cytoskeleton assembly, cell-cell attachment, and extracellular matrix remodeling4. TGF-B also induces anti-MET activity.

As TGF-B promotes metastasis, and its presence is a predictor of a negative outcome, this cytokine appears to be a suitable target for anti-metastasis therapies. Despite success in preclinical trials, anti-TGF-b pharmaceuticals have largely been unsuccessful in clinical studies. In a review by Teixeria et. al, the different kinds of anti-TGF-B pharmaceuticals have been explored to better understand why so few drugs that make it to clinical trials show any remarkable progress. The main focus of this microreview will be on the potential reasoning behind the poor success and how TGF-B could potentially be viewed as a friend, and not a foe.

**Recent Progress**

Currently, there are over 4497 clinical trials in place for colon cancer. However, the current methods of treatment for colon cancer are: surgery, chemotherapy, radiofrequency ablation, cryosurgery, radiation, targeted therapy, and immunotherapy. Targeted therapy includes monoclonal antibodies and immunotherapy include PD-1 and PD-L1 inhibitors. While the rate of new cases and death rate are on the decline, there is still need for more therapies outside of the traditional treatment. Rational treatment of cancer provides targeted therapy based on the characteristics of the cancer. As TGF-B has been seen as a predictor of poor outcome, there has been a growing interest to develop anti-TGF-B therapies.

**Anti-TGF-B Therapies**

Therapies have been developed to dampen the presence of TGF-B to enhance immune evasion and potential metastasis. There have been four main categories of anti-therapies which have been outlined by Teixiera et. al as (i) antisense oligonucleotides (ASOs), (ii) anti-integrins, (iii) ligand traps, and (iv) kinase inhibitors.

**Antisense Oligonucleotides**

The first category involves antisense oligonucleotides which are designed to dampen the expression of TGF-B by preventing TGF-B mRNA translation. Preclinical data exhibits reduced expression and in vivo, reduced tumor growth, and helps to prevent immune suppression as an effect of TGF-B. While this data appeared promising, Trabedersen shows little advantage in its antitumor effect, compared to standard chemotherapy. However, interesting enough, patients in phase II reported an improvement in cognitive function.

**Anti-integrins**

The second category of anti-TGF-B therapies includes drugs focused on anti-integrins. To activate TGF-B, the binding of integrins is important in the availability of TGF-B. This integrin activation of TGF-B has been found to be a positive feedback loop where TGF-B induces integrin expression. Anti-integrin therapies seek to block this feedback cycle and block the activation of TGF-B by the mediation of integrins. Antibodies have been employed to block integrins and have been found in preclinical models to reduce the growth of primary and secondary tumors. However, clinical studies did not find improvement in antitumor activity compared to standard chemotherapy.

**Ligand Traps**

The third group of anti-TGF-B therapies includes ligand-receptor interactions to block TGF-B signaling. Antibodies were employed against receptors and the use of ligand sequesters we also employed. Ligand sequesters were found to reduce the metastatic burden and angiogenesis in breast cancer models and also seemed to improve the cytotoxicity impact of natural killer cells. Antibodies reduced the growth of the primary and secondary tumors and also improved the cytotoxicity impact of natural killer cells. However, clinical trials failed to exhibit improvement.

**Kinase inhibitors**

The last and fourth category of anti-TGF-B therapies includes kinase inhibitors which block the binding of ATP to TGF-B receptors and dampen their kinase activity and ability to induce downstream signaling transduction. In mouse models, this form of anti-TGF-B therapies exhibited reduced tumor growth, and metastasis. However, this antitumor activity was only observed in 11% of patients in clinical studies.

**Discussion**

The lack of success in human, clinical studies highlights that there is a gap in knowledge of the mechanism TGF-B presents in human cancers. It is also possible that there has been an influence in the publication of positive results, giving bias towards treatment. Preclinical studies could be also looking over key differences between animal models and human models. As Teixeira et. al points out, animal studies typically begin anti-TGF-B treatment in animal models at an early stage. Certainly, we gain knowledge by determining if that anti-TGF-B pharmaceutical was effective in delaying or preventing metastasis. But these studies overlook one key reality of human models, early detection is not common in many patients presenting cancer tumors. Therefore, in human models, metastasis has already begun to occur and the process of EMT has already taken place. As mentioned before, TGF-B is a master inducer of EMT, but also acts as an anti-MET agent. By administering anti-TGF-B therapies too late, it could potentially disable the anti-MET capabilities of TGF-B and facilitate the proliferation and survivability of the secondary tumors. Therefore, timing in the administration of anti-TGF-B drugs is vitally important to consider. Furthermore, it could also be beneficial to consider TGF-B a friend in stage 4 cancers rather than a foe for its anti-MET activity. Another key feature is that TGF-B signaling is opposite to BMP signaling which is a MET inducer. By targeting TGF-B, BMP should increase by antagonist effect and effectively increase the promotion of MET which could be contributing to the metastatic development in cancers. The role of TGF-B in human cancer-associated fibroblasts should be better analyzed in order to gain a clearer picture of what therapies can be implemented and the procedure for administration. While TGF-B is a predictor of a poor prognosis, there is a clear obstacle in anti-TGF-B therapies. They appear promising, however, a different approach is needed.
Until then the treatment of colorectal cancer is kept to the traditional methods.

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