SHORT COMMUNICATION

Repurposing Cancer Drugs for Type 1 Diabetes Prevention

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DESCRIPTION

Type 1 Diabetes (T1D) is an incurable, chronic autoimmune disorder characterized by destruction of insulin- secreting pancreatic β cells by diabetogenic T cells [1-3]. Despite affecting three million Americans, there is currently no preventive measure for this disease [2]. In 2022, Taplizmab became the first and only FDA-approved drug to significantly delay the onset of T1D [4]. However, due to the heterogeneity of T1D and the necessity of antibody infusion in children, the development of additional drugs to delay the onset and ultimately prevent T1D is urgently needed.

Cancer drugs targeting rapid proliferation for T1D prevention

To prevent T1D, it is essential to shield insulin-producing pancreatic β cells from destruction by self-antigen activated T cells [1-3]. Similar to many cancer cells, diabetogenic T cells exhibit glycolysis, resembling the Warburg effect, to sustain their rapid proliferation [5-8]. When naïve T cells are activated to become effector T cells against pancreatic β cells, they go through metabolic switch from oxidative phosphorylation to aerobic glycolysis (**Figure 1**).

In contrast, terminally differentiated memory T cells uses oxidative phosphorylation [5,6]. Cancer drugs targeting high proliferation rate, stimulation, and glycolysis can potentially target diabetogenic T cells and prevent T1D without minimal effects on naïve or memory T cell population [9-15] (**Figure 1**). Utilizing cancer drugs already in clinical trials or FDA-approved provides the advantage of having existing efficacy and safety data in humans.

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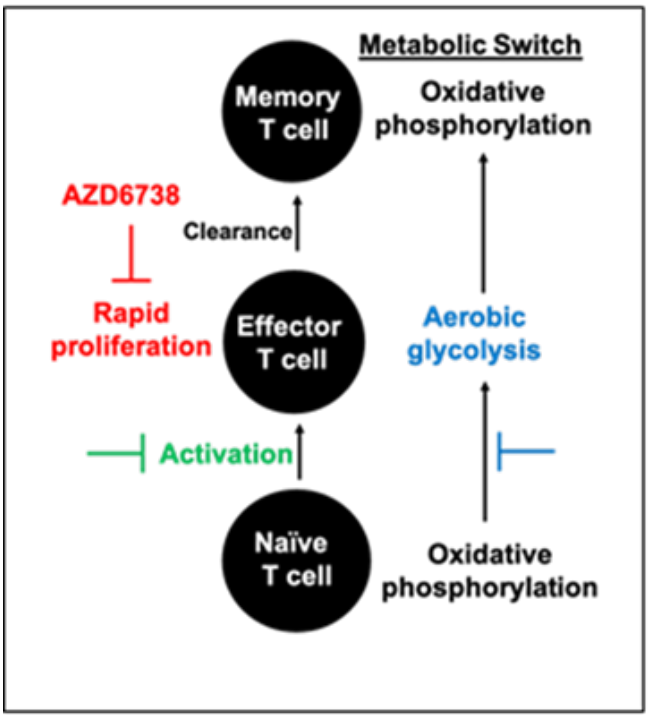

Figure 1. Potential targets for diabetogenic t cell inhibition for T1D prevention.

A cancer drug ceralasertive (AZD6738) prevents T1D in a mouse model

We recently reported a study in Frontiers in Immunology titled "An orally available cancer drug AZD6738 prevents type 1 diabetes", detailing our efforts to repurpose AZD6738 for T1D prevention [16]. AZD6738, an oral inhibitor of ataxia telangiectasia mutated and Rad3-elated (ATR) kinase, is currently in phases I and II clinical trials for multiple cancers [17-21]. In this study, AZD6738 effectively prevented T1D in an adoptive transfer mouse model by inducing specific cell death in rapidly proliferating diabetogenic T cells [16]. Its mechanism of action mirrors its impact in cancer, involving excess DNA replication origin firing in rapidly proliferating T cells, resulting in DNA damage accumulation, IFNγ production inhibition, and reduced proliferation [16,22]. Importantly, even with an extended treatment period of up to 5 weeks,

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AZD6738 demonstrated no adverse effects [16]. The oral availability of AZD6738 is advantageous, particularly for patients where antibody infusion is not preferred option.

Future of AZD6738 in T1D prevention

Given that this study is in its early stage, there are many hurdles to pass for AZD6738 to be applied in human T1D prevention. The verification of whether self-antigen-activated T cells resurge from the naïve T cell pool needs confirmation, in a spontaneous disease model, as the adoptive transfer model utilized in this study lacks endogenous naïve T cells [23,24]. Highly proliferative T cells are susceptible to AZD6738, with effector T cells reported to undergo up to four divisions daily, a rate faster than many activated leukocytes or cancer cells [22,25-29]. However, thorough investigation into potential off-target effects on other cell types is essential prior to human application. A subpopulation of memory T cells crucial for host-defense can proliferate rapidly, potentially making them susceptible to damage by AZD673830. Therefore, designing the treatment schedule will be crucial to maximize diabetogenic T cell inhibition while mitigating the risk of myelosuppression, reported in some cancer clinical trials involving extended treatment periods [30-32].

Other cancer drugs and combination therapy to consider for T1D prevention

Combination therapy is designed to enhance potency by employing multiple agents, enabling the use of lower doses of each, thereby reducing potential toxicity [33-35]. In cancer clinical trials, AZD6738 is frequently combined with other anti-cancer agents [18,36,37]. The specificity of AZD6738 towards highly proliferative cells makes it advantageous for combination with glycolysis inhibitors in T1D prevention. While both agents target diabetogenic T cells, they address different aspects AZD6738 focuses on the high proliferation rate, while glycolysis inhibitors address the transition to aerobic glycolysis metabolism (Figure 1). One potential candidate for combination with a proliferation inhibitor like AZD6738 is the glycolysis inhibitor PFK15 [12]. PFK15 has demonstrated a significant delay in the onset of T1D by inducing terminal exhaustion in diabetogenic T cells in an adoptive transfer mouse model [38]. Combining AZD6738 and PFK15 may permit the use of lower doses for each agent, enhancing their diabetogenic T cell inhibition activity. Given that AZD6738 does not impact T cell activation [16,22], it may also be combined with drugs targeting activation [15]. Besides AZD6738, several FDA-approved or clinically-trialed DNA replication inhibitors show potential for preventing or delaying the onset of T1D [39-43]. For instance, methotrexate, known for its ability to inhibit T cell proliferation, has been successfully repurposed for treating another autoimmune disorder, rheumatoid arthritis [39]. While further investigation is needed to assess its impact on T cells, imatinib has demonstrated the prevention of pancreatic β cell apoptosis [44].

The exploration of cancer drugs targeting DNA replication for T1D prevention, exemplified by AZD6738, is a promising avenue in pre-clinical studies. Inhibition of T cell proliferation, glycolysis, or activation may collectively contribute to prevent T1D while mitigating off-target effects. The repurposing of existing cancer drugs opens up possibilities for novel therapeutic strategies in the prevention of T1D.

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