Introduction

Trichosanthin (TCS), known as a plant toxin, is applied as a midterm abortifacient in clinics, and currently reported to exhibit other biological and pharmaceutical effects such as anti-tumor, anti-HIV, and immunoregulation. TCS was found out to firmly inactivate the ribosomes of the eukaryotic cell, but this finding was far enough to explain its various biological and pharmaceutical effects. Our previous studies focused on exploring novel TCS binding proteins, as to reveal new mechanisms in mammalian cells. And we found out that TCS and cation-independent mannose-6-phosphate receptor (CI-MPR) competitively bind to Golgi-localized, γ-ear containing and Arf-binding proteins (GGA), which finally increased the cell permeability of Granzyme B and promoted the cytotoxic T lymphocyte-mediated tumor cell apoptosis.

Keywords: Trichosanthin; Granzyme B; anti-cancer effects

To cite this article: Yinxin Zhu, et al. Trichosanthin induces anti-cancer effects by increasing the penetration of granzyme B into tumor cells. Can Cell Microenviron 2017; 4: e1576. doi: 10.14800/ccm.1576.

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into target cells \[^3\]. After entry into cytosol, TCS was believed by most studies to inactivate ribosome, subsequently hampered protein synthesis and exert anti-tumor effects. Yet, this mechanism actually is far enough to explain the complicated anti-tumor effects of TCS. Cui L et al in 2015 reported that TCS can significantly increase the expression Smac, a mitochondrial protein, which helps to reverse TCS resistance in CaSki cervical cancer cells \[^4\]. Studies then found out that TCS could induce autophagy in gastric cancer cell MKN-45 by activating reactive oxygen species (ROS) and NF-κB/p53 pathway \[^5\]. Miao J et al indicated that TCS can suppress the proliferation of glioma cells through inhibiting LGR5 expression and the Wnt/β-catenin signaling pathway \[^6\].

Our recently published study used pull down assay and identified TCS binds with Golgi-localized, γ-ear containing and Arf-binding proteins (GGA) proteins in HepG2 cells \[^7\]. GGA contains four structural functional domains, of which the N-terminal Vps, Hrs and STAM (VHS) domain can bind to DXXLL motifs of cargo proteins and was confirmed in our study to directly interact with TCS \[^7\]. TCS then can competitively inhibit cation-independent mannose 6-phosphate receptors (CI-MPRs), a transmembrane glycoprotein, binding to GGA. And such competitive inhibition increased the accumulation of CI-MPRs on the cell surface, and subsequently improved the permeability of tumor cells to Granzyme B (GrzB), as CI-MPR has been identified as a death receptor for GrzB binding and uptake \[^7\]. GrzB is one of the critical effectors released by cytotoxic T lymphocytes (CTLs) and can induce the apoptosis of target cells. Thus, we here revealed out that TCS induced anti-tumor effects through competitively inhibiting the binding of CI-MPRs to GGA, subsequently increased its translocalization onto the cell surface and mediated the uptake of GrzB into target cells, and finally activated cytotoxic T cell-induced apoptosis.

Above is indeed described a newly discovered mechanism for TCS to promote CTL-mediated immunotherapy in tumors by inducing apoptosis. TCS-induced apoptosis has already been observed in breast cancer cells both in vitro and in vivo models \[^8\]. Zhang D et al then reported that low concentration of TCS induce apoptosis and cell cycle arrest via c-Jun N-terminal protein kinase (JNK) /mitogen-activated protein kinase (MAPK) activation \[^9\]. Besides the activation of intracellular apoptotic signaling pathways, TCS was firmly described to increase the percentage of effector T cells, particularly interferon-gamma (IFN-γ) producing CD4+ and CD8+ T cells, in the lewis lung cancer-bearing mouse model, and then enhance the anti-tumor response and induce immune protection by boosting the interaction between TSLC1 and CRTAM \[^10\]. Thus TCS can exert its anti-cancer effect by enhancing the immuneresponse against tumor cells.

However, as early in 1990s, TCS was reported to suppress mitogenic, antigenic, and allogeneic responses of human lymphocytes and thus can induce immunosuppression \[^11\]. Later studies demonstrated that DQ alleles play a critical role in TCS-induced immunosuppression by down-regulating function of CD8 cells \[^12\], and depletion of CD8 cells from total T cells or blocking expression of HLA-DQ molecules could effectively diminish TK’s inhibitory activity against immune response \[^13\]. Recently, Yang N et al reported that a TCS-derived peptide can suppress type 1 immune response by TLR2-dependent activation of CD8(+)CD28(-) tregs \[^14\], and suggest new eras in using TCS-tPN, a homo-tetramer, as a therapeutic reagent for Th1-dominant immunological diseases \[^14\] and inducing tolerance of cardiac allografting \[^15\]. And studies in major histocompatibility complex-mismatched mouse skin allograft also revealed the inspiring results of TCS effectively preventing allograft rejection, perhaps by reducing IL-2 and IFN-γ expression and inducing IL-4 and IL-10 expression \[^16\]. Thus, it seems really a complicated process as to clarify the involvement of TCS in immunoregulation, which sheds new areas for us researchers to explore.

**Conclusion**

Trichosanthin, a component extracted from Chinese medicine herb Trichosanthes Kirilowii, exhibited effective anti-cancer effects through various mechanisms as been reported by now. Our group recently reported the pro-apoptosis effects of TCS in HepG2 cells mediated by cytotoxic T cells and GrzB, and added new blocks into the anti-cancerous mechanisms of TCS.

**Conflicting interests**

The authors have declared that no conflict of interests exist.

**References**


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