1. Angiogenesis is essential for tumor growth and TECs have unique characteristics

Angiogenesis is required for tumor progression and metastasis[[1]](#endnote-1). Tumor cells secrete vascular endothelial growth factor (VEGF) to induce angiogenesis to provide oxygen and nutrients for tumor development.[[2]](#endnote-2) Excess VEGF in tumors drives aberrant angiogenesis to increase vascular permeability and interstitial fluid pressure (IFP), leading to disordered vascular structure[[3]](#endnote-3). In 1971, Dr. Judah Folkman and his colleagues introduced the concept of anti-angiogenic therapy which has become a significant aspect of cancer treatment[[4]](#endnote-4). The angiogenesis inhibitors, such as bevacizumab, a neutralizing antibody targeting VEGF, exert their anti-tumor effects by disrupting tumor blood supply[[5]](#endnote-5). They also normalize vascular structural abnormalities caused by excess VEGF and improve drug delivery to cancer tissue and immune cell mobilization[[6]](#endnote-6). It has been shown to improve outcomes in cancer patients when used in combination with anticancer agents and/or immune checkpoint inhibitors[[7]](#endnote-7). However, VEGF targeting is non-specific as normal physiological angiogenesis in normal endothelial cells (NECs) also requires VEGF[[8]](#endnote-8). NECs and tumor endothelial cells (TECs), which line blood vessels in tumor tissues, show different in terms of gene expression profile[[9]](#endnote-9), pro-angiogenic properties[[10]](#endnote-10), sensitivity to drugs[[11]](#endnote-11) and so on. Due to various side effects associated with anti-VEGF therapy[[12]](#endnote-12), it is crucial to explore novel approach to inhibit angiogenesis that target TECs independently of VEGF signaling.

1. Introducing the relationship between inflammation and thrombosis

In 1863, Rudolf Virchow proposed the correlation between inflammation and carcinogenesis[[13]](#endnote-13). Tumors have been described as 'wounds that never heal'[[14]](#endnote-14)~~.~~ In recent years, it has been demonstrated that tumor-associated chronic inflammation promotes immunosuppression of the tumor microenvironment and tumor progression[[15]](#endnote-15).  The study indicates that TECs augment pro-inflammatory signaling and invasiveness in cancer cells[[16]](#endnote-16). This augmentation includes the activation of integrins[[17]](#endnote-17), a significant increase in nuclear localization of NF-κB-p65 and pSTAT3[[18]](#endnote-18), and elevated expression of pro-inflammatory cytokines[[19]](#endnote-19), exemplified by high levels of tumor necrosis factors (TNFs) and interleukins (ILs). Additionally, there is an upregulation of pro-inflammatory cell adhesion molecules, such as selectins and intercellular adhesion molecule (ICAM)-1[[20]](#endnote-20). Leukocytes often aggregate around tumor blood vessels[[21]](#endnote-21) and stimulate angiogenesis and tumor metastasis[[22]](#endnote-22). Numerous studies have confirmed that thrombosis is a common complication in cancer patients and is the second leading cause of cancer deaths[[23]](#endnote-23). Inflammatory cytokines promote the procoagulant phenotype of endothelial cells (ECs) and promote platelet activation[[24]](#endnote-24). TNF-α and IL-1β induce the expression of tissue factor (TF) and von Willebrand factor (vWF) on ECs[[25]](#endnote-25). Tumor-derived factors also stimulate neutrophils to release their DNA and thus form chromatin networks known as neutrophil extracellular traps (NETs). Many studies showed the involvement of NETs in platelet thrombus formation and the activation of the coagulation cascade[[26]](#endnote-26). This interrelationship between inflammation and thrombosis highlights the importance of studying both aspects in the context of cancer.

1. EGCG anti-inflammation effect

Epigallocatechin gallate (EGCG) is the most abundant polyphenolic compounds in green tea. EGCG has been reported as a natural antioxidant and anti-inflammatory[[27]](#endnote-27) agent in the treatment of cancer[[28]](#endnote-28) and multiple diseases[[29]](#endnote-29)[[30]](#endnote-30)[[31]](#endnote-31)[[32]](#endnote-32). One of the anti-tumor effects of EGCG is mediated by acting as a strong oxidant by scavenging ROS and chelating free transition metals[[33]](#endnote-33), and inhibit tumor inflammation by inhibiting the NF-κB pathway[[34]](#endnote-34). We previously reported that EGCG inhibited TEC proliferation and migration, but not NEC[[35]](#endnote-35). However, the anti-inflammatory effect of EGCG on TEC is currently unclear.

1. Introduction of EGCG-MEND

To achieve the strategy of targeting TECs with EGCG for anti-inflammation, we need to deliver EGCG to TECs. We previously developed drug delivery system (DDS) with lipid nanoparticles of MEND (Multi-Enveloped Nanodevices: MEND)[[36]](#endnote-36). Binding of cyclo(Arg-Gly-Asp-D-Phe-Lys) (cRGD) to MEND[[37]](#endnote-37) resulted in the specific delivery of the content of the MEND to TEC, because the receptor for cRGD is an α V β 3 integrin, which is selectively highly expressed in TEC[[38]](#endnote-38). We previously demonstrated the therapeutic efficacy of MEND with silencing vegfr2[[39]](#endnote-39) or biglycan[[40]](#endnote-40) genes in TECs using mouse tumor models. Targeting vegfr2 in TECs inhibit tumor angiogenesis and tumor growth 29, confirming the therapeutic effect of targeting VEGF signaling[[41]](#endnote-41). In addition, biglycan which is highly expressed in TECs is involved in tumor angiogenesis[[42]](#endnote-42), tumor blood vessel destabilization and metastasis[[43]](#endnote-43). RGD-MEND containing biglycan siRNA specifically delivered tumor blood vessels, inhibited tumor growth and normalized tumor blood vessels with increasing pericyte coverage30. This RGD-MEND system is useful proving drug effects on TEC specifically. In this study, we demonstrated the specific effect of EGCG on TEC using RGD-MEND by inhibiting TEC inflammation and thrombus formation as a novel strategy of cancer treatment.

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