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Review

The Impact of OPIUM and Its Derivatives on Cell Apoptosis and Angiogenesis

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HIGHLIGHTS

- Opium can initialize cell death through activation of apoptotic events which in turn induces cascade pathways of angiogenesis.
- Opium and its derivates such as morphine, codeine, noscapine, and papaverine increase the rate of cellular apoptosis and angiogenesis through various mechanisms in most cells.
- Opium and its derivates can disrupt an organ's normal function.

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ABSTRACT

Opium is an opiate substance with a significant effect on human physiology and behavior. Ancient priests used opium as a powerful healing drug and many medical texts have referred to opium as medication, especially during the nineteenth century. In old days, the medical use of opium was popular and was called "God's medicine". On the other hand, understanding the molecular pathway of opium function within cells is very essential from pathophysiological views and clinical applications. The current literature shows that opium can initialize cell death through activation of apoptotic events, which in turn induces cascade pathways of angiogenesis. In this review article we attempt to investigate the effects of opium on cell apoptosis and angiogenesis.

Keywords: Opium; Apoptosis; Morphine; Angiogenesis

Introduction

Opium with a bitter taste is an opiate substance that is derived from a plant with the scientific name of Papaver Somniferous from the Papaveraceous family. Opium's natural and synthetic derivatives have significant effects on human physiology and behavior (1, 2). The opium plant's ovary contains poppy seeds with an oval shape and pink petals. When the petals wither, using a traditional blade, farmers seep through the immature ovary and let the secretion coagulate in the vicinity of the air. After a full day and night, the opium gum turns brown and sometimes black. The gum remains attached to the outer wall of the

ovary, so the farmers can scrape and collect it easily. Opium has different usual names, such as Papaver Somniferous and Poppy in English and Khashkhash in Persian. The original name comes from the Greek word "Theriaca". In Arabic, it is called Teryaqi, abion and opium, while abion is derived from the Greek root opium. In fact, it is a substance with a wide varieties of pharmacological and pathological effects due to its twenty types of alkaloids and other seventy compounds (3). Opium is a natural latex with 12% morphine. Physically, opium comes in various forms of naturally (Raw, juice, burnt opium), semi-synthetic (Medications such as morphine, codeine, hydrocodone, oxycodone), and fully synthetic (Drugs like fentanyl, fentanyl analogues, tramadol, and mostly methadone) (Figure1).

The left-over material after smoking is a brown and shiny substance called "burnt opium", which is soluble in the water to reuse.

Addicts dissolve the burnt opium in the water and boil it for reusing. Then it is passed through a strainer to produce pulp. Consumers reheat the pulp to make a thick and brown paste called "juice". This juice is much effective than opium and is consumed orally or by smoking.

History of opium

The Sumerian, Greek, Egyptian, Persian, Assyrian, Roman, Minoan, Arab, and Indians have used opium since 5000 BC. Opium has been cited and explained in the ancient medical books by Persian physicians like the famous Avicenna as an analgesic and antitussive. It was suggested for the management of neuromuscular disturbances, sexual dysfunction, and hypnosis. Muhammad ibn Zakariya al-Razi another Persian physician and Abu al-Qasim al-Zahrawi the Andalusian ophthalmologist also recommended opium as anaesthetic for surgical procedures. In the 14th century, the Ottoman Empire recruited opium to manage diseases such as sciatica pain, migraine, and the same occasions. Medical use of opium in the 19th century was particularly popular and users called it the "drug of God". The first pure naturally derived medicine and the first to be commercialized of opium was in the 16th century. After that Thomas Sydenham who was known as Plato of England, developed a new drug from opium in the 17th century, which was later called morphine.

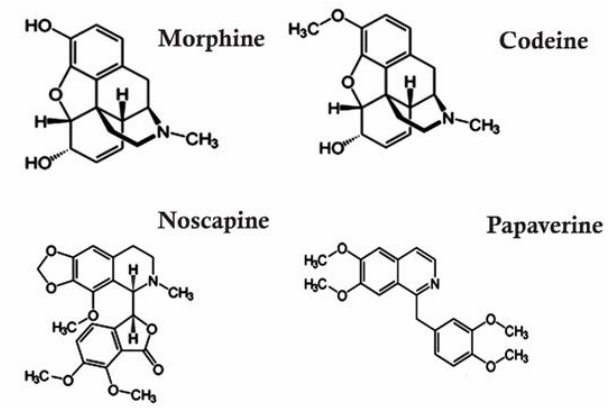

Figure 1. Molecular structures of opium alkaloids

Opium compounds and their function in different body tissues

Several studies have shown that opium interferes with the symptoms of prostate cancer, so it may delay the early detection of this disease. Opium usage was found to be related to a remarkable decline in the prostate-specific antigen (PSA) serum level (4). It has been observed that opium derives cause changes in male sex hormones and function through testicular tissues including Sertoli cells and seminiferous tubules resulting in spermatogenesis and fertility problems (5-7). There are some evidence that the diameter of the sperm-producing tubes becomes narrower in opium addict patients (8).

Opium derives can change the normal pituitary system function and daily methadone intake for 5 to 10 days could significantly decrease the weight of genitals in rats. It is found that opiates had an inhibitory effect on Gonadotropin-releasing hormone (GnRH) secretion and remarkably reduced testosterone secretion (9). Ranji and his colleagues showed that the semen analysis of heroin addicts was completely abnormal due to heroin toxicity for the reproductive system (8).

On the other hand, morphine consumption can cause structural abnormalities in gastrointestinal and kidney tissue. Inhalation of opium can increase the production of inflammatory cytokines; and also, it may cause hypoxia by elevation of carboxy-haemoglobin, which increases erythropoietin production, followed by polycythaemia with iron overload. Using opium directly or indirectly affects the function of various tissues in the body including white blood cells. Although blood cells have a short lifespan, they have been shown to have opioid receptors (σ, μ, and κ), so are able to respond to endorphins (β-endorphin, dynorphin, Met-enkephalin) (10, 11). Occupation of opioid receptors by endorphins or opioids has a direct effect on the levels of cytokines, cell growth, cell division, and differentiation of peripheral white blood cells. This in turn may cause hepatic failure. Mazumder and colleagues showed that fatty liver and liver fibrosis were more prevalent among opium abusers (12). There is some evidence of relationship between oesophageal cancer and polyneuropathy, which both are common in opium abusers (13, 14). Some researchers also found a relationship between opium consumption and oesophageal, laryngeal, and bladder cancers to some extent (14, 15).

The negative impact of opium on the immune system can be explained by decreasing *Interleukin-2 (IL-2)* at the heterogeneous nuclear RNA (hnRNA) (11, 16), which has been scientifically proven. A slight increase in IL-2 and a significant decrease in IL-10 happens in addicted ones, which affects their immunity against infections. In these people, the process of differentiation in cell-assisted lymphocytes (Th) is switched from Th2 to Th1(11, 17). Bhat et al. have concluded that an increase in TGF-β1 occurs in opium users, which is a result of morphine intake, and it leads to initiation of the planned death (apoptosis) of the macrophages (18). The TGF-β1, a transforming growth factor-beta superfamily of cytokine (Th3) (19, 20), is involved in the regulation of the immune system (19, 21), macrophages apoptosis (18), and the suppression of TH1(20). Malik et al., have shown that if morphine is exposed into the bone marrow, then it causes cell death apoptosis in 20% of bone marrow cells that this might be another reason for a decrease in the number of red blood cells among addicts (22). Therefore, opium smokers have higher levels of Th2 and Th3-helping lymphocytes in comparison with normal people. This means that their Th1-assisted lymphocytes are less effective, and are more likely to be damaged during infection because of lower activity of Th2, and higher activity of Th1.

Morphine can increase platelet adhesion and aggregation; and intracellular calcium (23, 24), which results in the formation of plaques. This process results in a significant decrease in platelets, so opium can lead to haemolysis.

The use of opium causes changes in the immune responses to stresses that can be resulted in damaging tissues via alteration in the secretion of cytokines (25). Similarly, other opioid derivatives such as morphine, noscapine, papaverine, and codeine, which are the major constituents of opium, can also affect the production and release of cytokines including interleukin-4 (IL-4) and interferon-gamma (IFN-γ). These can also act as either stimulants or inhibitors of inflammation (25). A 2015 study by Asadi Karam et al., has shown that opium is able to stimulate secretion of pro-inflammatory cytokines INF-γ, Tumor Necrosis Factor-alpha (TNF-α) in human that was able to suppress the secretion of anti-inflammatory cytokines like IL-4 and IL-10 (26). Another research by Lashkari Zadeh et al., studied the effect of opium on the level of inflammatory cytokines in male rats after surgery, which showed that opium addiction significantly increased the level of INF-γ(27) pro-inflammatory cytokines and decreased the levels of IL-4 (28) anti-inflammatory cytokines after surgery (29).

C-reactive protein (CRP) is one of the acute phase proteins of inflammation and is used as an inflammatory marker in diagnosis of inflammatory infections. Plasma CRP levels (30) can play the role of a marker in the pathogenesis of cardiovascular diseases that affects the complement system. In bacterial and viral infections, active rheumatic fever, acute myocardial infarction, stroke, rheumatoid arthritis, etc, plasma CRP levels are increased in the serum of individuals (31). It has been observed that opium consumption increases the levels of cytokines including IL-17, IL-10, and TNF-α and inflammatory markers CRP, C3 and C4 complement and immunoglobulin A (31, 32). A study on opium-addicted men also found that serum levels of IL-4, INF-gamma, were lower than healthy cases, while levels of TGF-β and IL-6 were higher (25).

Opium and apoptosis

Apoptosis: Apoptosis is a highly conserved pathway that causes programmed cell death and is essential for the balance of body tissues. This mechanism is a fundamental component of many of the body's normal physiological processes including embryo formation, normal tissue development, and immune responses (33). This pathway possesses a variety of interfaces between intracellular cascades and is generally divided into two Extrinsic and Intrinsic pathways (Figure 2).

Opium causes cell death through apoptosis and researches have shown that apoptosis massively happens in the brain and liver of opium-addicted rats (34). Opium has been observed to stimulate apoptosis through both extrinsic and intrinsic pathways in Jurkat cells. Although it increases the expression of some anti-apoptotic molecules that might be a normal reflection of the cell's resistance against death, use of opium derivate as a treatment can stimulate apoptosis in liver and brain cells in Rat's Jurkat cells (35).

The extrinsic pathway starts with stimulating death receptors (such as TNF-R, FAS) and then activating

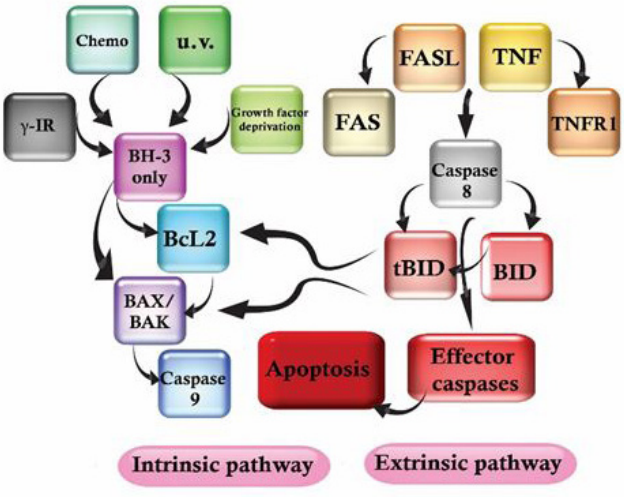

Figure 2. Two Extrinsic and Intrinsic pathways of apoptosis

Caspase 8 and its downstream effectors, however, this cascade can be inhibited by (CFILP) and (IAPs). The intrinsic pathway is stimulated by environmental factors such as cellular stress, DNA damage, and hypoxia, and is followed by releasing cytochrome C from mitochondria, which functions as an electron shuttle in the respiratory chain and interacts with cardiolipin. Subsequently, Caspase 9 and other downstream caspases are activated in the early stages of apoptosis. These proteins destroy key cellular constituents including structural and skeletal proteins and other major proteins such as DNA repair enzymes (36). Apoptotic stimulating agents are BID, BAX, BAD while survivin and Bcl-2 proteins are anti-apoptotic. The Bcl-2 protein family is a critical regulator of apoptosis within the mitochondrial outer membrane and can inhibit the internal pathway of apoptosis

In addition, it has been observed that opium addicts frequently suffer from infectious diseases due to poor immune responses (25, 32). Thus, it seems that opium can induce in-vivo and in-vitro apoptosis in immune cells through an unknown pathway (25). It has been found that the expression level of pro-apoptotic molecule ABL1 was increased in Jurkat cells treated with opium. ABL1 is a cytoplasmic and nuclear protein of tyrosine kinase that is involved in various cellular functions including division, differentiation, adhesion, and response to cellular stress (37).Study on Jurkat cells treated with opium showed that the mRNA expression level of pro-apoptotic molecules such as *LTA, TP53BP2, BNIP3, TNFRSF1, Bcl-2,* and *NOD1* increased by two-fold. It is believed that increased expression of *BNIP3* and *Bcl-2* levels triggers apoptosis in opium-treated cells. The TNF/TNFR1, LTA/TNFR1, and LTA/LTBR pathways also play significant roles in the initiation of apoptosis in the Jurkat cell line, when they are exposed to opium. The apoptotic properties of opium-treated Jurkat cells lead the mRNA expression level of some anti-apoptotic molecules such as NOL3, Bcl-2, and DFFA to increase inside cells.

Opium also increases TP53 apoptotic properties by promoting its function rather than its expression. In addition, the expression levels of *caspase 3 (CASP3), CASP4,* and *CASP6* increase after treating cells with opium. It mainly induces cellular apoptosis through the extrinsic pathway, which is led by the expression of *TNFRSF1A* and *LTA* molecules.

Noscapine: Noscapine is an opium alkaloid with chemical similarity to podophyllotoxin and colchicine, which keeps cells in the mitosis stage leading towards apoptosis. Previous studies have shown the effects of alkaloids such as morphine, heroin, codeine, noscapine, and papaverine on apoptosis (35). It has been shown that noscapine could effectively inhibit the proliferation of LoVo cells in vitro, and enhance the anticancer effects of several chemotherapy drugs by inducing apoptosis in malignant cells without any detectable toxicity to the normal cells. It has been shown that *Bax* and *cytochrome c (cyt-c)* gene expression, survivin and *Bcl-2* gene expression, as well as caspase-3 and caspase-9 activation, are increased along with an increase in chromatin density and fragmentation. Noscapine induces apoptosis in colon cancer cells with mitochondrial pathways and halts phase M/G2 by causing chromatin condensation and nucleus scattering. It is believed that tumorigenicity is also inhibited by noscapine (38).

Morphine

Morphine and similar opioids, which are medically used as analgesic drugs, are able to bind to specific receptors in different tissues and to induce apoptosis (39, 40). Morphine has its highest pharmacological effects on the central nervous system and gastrointestinal tract (41), however, some other researchers suggest a protective role for morphine (42). It has been observed that morphine could cause the death of neurons by decreasing the level of intracellular dopamine, which is associated with increased cellular metabolism and oxidative damage to the cells (43). Repeated injections of opioids such as morphine alter the expression of genes in different areas of the brain that is resulted from the activation of multiple transcription factors in response to morphine sensitivity and resistance (44). There are many extra- and intracellular signaling substances that induce apoptosis through the receptors at the surface of cells (44), and morphine is one of them (41, 45). Studies have also shown that long-term treatment with morphine in mice led to changes in apoptotic factors. These changes include increased levels of the FAS receptor (pro-apoptotic factor) and decreased level of Bcl-2 (anti-apoptotic factor), especially in the brain (41). Injection of morphine has also been shown to increase pro-apoptotic proteins (caspase-3, Cysteinyl Aspartate-Specific Protease, and Bax and a decrease in Bcl-2 protein (anti-apoptotic) in rat spinal cord (46) (Figure 3).

The Effect of Morphine on Alteration of Bax/ Bcl-2 Apoptosis Factor

Bcl-2 Family proteins (B-cell lymphoma 2) are a group of proteins, which include anti-apoptotic (Bcl-2, Bcl-XL) and pro-apoptotic (Bcl-2 associated x protein, Bax) factors. The sensitivity of the cell to apoptosis is regulated by balancing between pro-apoptotic and anti-apoptotic factors of the Bcl-2 family (33, 47) and in this system the Bcl-2 protein with a 28-kDa anti-apoptotic unit prevents cell death. It is observed that the ratio of Bax/ Bcl-2 proteins is increased by morphine. Long-term treatment of morphine increases pro-apoptosis protein factor FAS receptor (pro-apoptotic factor) and decreases protein factor Bcl-2 (anti-apoptotic factor), which together

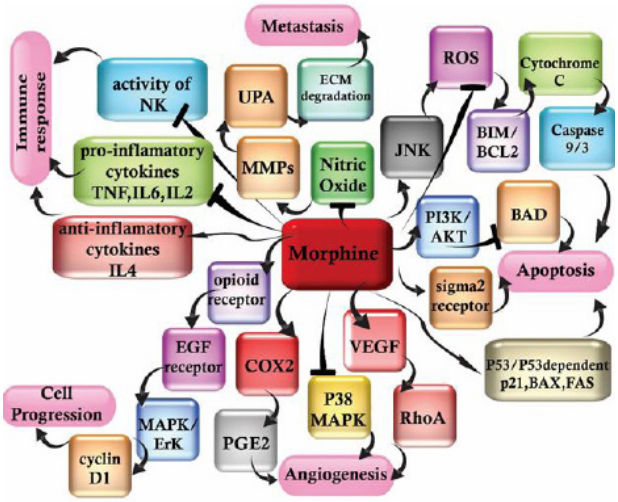

Figure 3. Morphine can have an inhibitory effect on cellular immune response in several ways: 1. by inducing anti-inflammatory cytokines, 2- With inhibitory effect on pro-inflammatory cytokines such as interleukin 2, interleukin 6 and TNF, and 3- With the effect of inhibiting the activity of NK. Morphine, on the other hand, can induce angiogenesis by inducing VEGF and COX2, as well as inhibiting P38 MAPK. Morphine can have a positive effect on cytochrome c and caspase 3 and 9 by inducing P53, P21, Bax, and Fas cascading pathways, as well as inducing JNK, ROS, Bim/Bcl2, and directing the cell toward apoptosis. Morphine also affects the matrix of metalloproteinases, as well as ECM, by reducing and inhibiting nitric oxide, and initiates cell metastasis. NK: Natural Killer Cells; VEGF: Vascular endothelial growth factor; COX2: Cyclooxygenase 2

induce apoptosis in rat's brain (41).

Morphine and DAMGO (D-Ala, N-MePhe, Gly-Ol-enkephalin), a synthetic opioid peptide with high μ-opioid receptor specificity, have been shown to induce apoptosis in T lymphocytes by a decrease in Bcl-2 anti-apoptotic protein expression plus an increase in pro-apoptotic Bax expression (48). It seems that via Delta Receptors, Opioids inhibit FADD (Fas-Associated protein with Death Domain) by activating the signaling axis of ERK1/2 and blocking the vital cell signaling axis while no inhibition was observed in Delta-free mice (49) indicating the role of Delta receptors.

Effect of Morphine on Caspase-3 Apoptosis Factor Change

It is been found that morphine significantly increases fractured caspase levels, while Caspase-3 is one of the active caspases, which plays an important role in the internal and external pathways of apoptosis. PARP (Poly ADP ribose polymerase) is a protein that binds to single-stranded DNA and plays a role in its repair process. PARP has three subunits of 24, 89, and 116 Da that subunits24 and 89 induce apoptosis by activating caspase-3. PARP is a substrate of specific caspases such as caspase-3 and Caspase-3 can decompose PARP in its active form. The amount of PARP protein significantly increases.

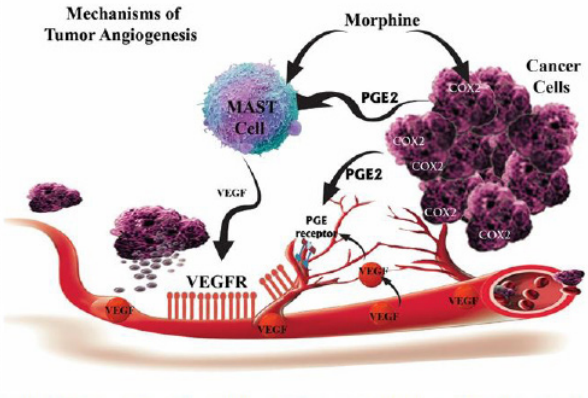

Figure 4. Mechanisms of tumor angiogenesis: Morphine has a direct effect on COX-2 and the production and secretion of prostaglandins, increases VEGF and induces angiogenesis. VEGF: Vascular endothelial growth factor; COX2: Cyclooxygenase 2

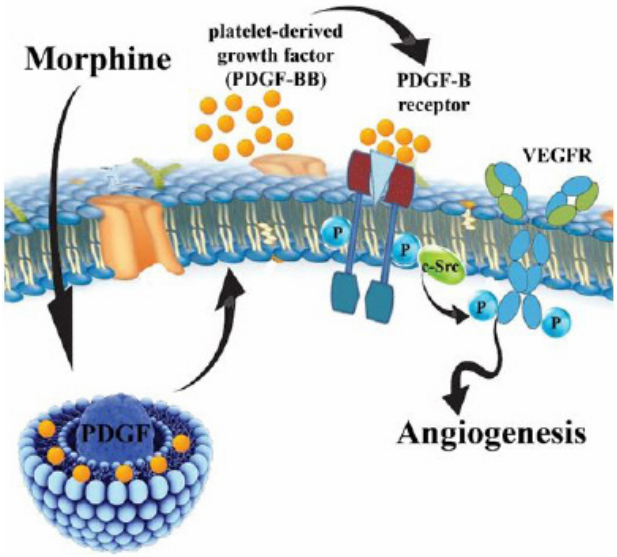

Figure 5. Morphine induced angiogenesis by the signaling pathway of PDGF/PDGFR/c-Src

Morphine and angiogenesis

Angiogenesis means the creation of new capillaries from existing vessels. Angiogenesis is a physiological regeneration process, which is mediated by a balance between angiogenesis promotor and inhibitor factors. In some malignant conditions, the balance is lost and tumor growth or metastasis happens. Koodie et al. showed that morphine could repress vascular endothelial growth factor (VEGF) transcription and provokes the secretion of transcription factor1 alpha (HIF-1alpha)/p38MAPK via a hypoxia-inducible pathway in mouse Lewis lung carcinoma cells (LLCs)(50) (Figure 4). Morphine induces PDGF/PDGFR/c-Src signaling pathway in angiogenesis followed by activation of AKT and ERK1/2 molecule, which is a result of releasing and activating endothelial platelet-derived growth factor (PDGF-BB) receptors.

It has been found that c-Src kinase can activate VEGF and its receptor (VEGFR), which is followed by the initiation of theangiogenic signaling pathway of up-regulated VEGFR that in turn results in angiogenesis (51). on the other hand, morphine amplifies tumor angiogenesis by enhancing the strength of mast cells. Previous studies have shown that the angiogenic potential of cells in prostaglandin E2 (PGE2) was improved resulting in VEGF synthesis.

Morphine can also cause over-expression of the inflammatory cyclooxygenase 2 (COX-2) and release of PGE2 from the tumor cells ending in the production of tumor vessels (51). However, a study by Sabrina Bimonte and colleagues showed that morphine improved the angiogenesis and progression of human breast carcinoma cells in xenograft mouse model (52) (Figure 5).

Conclusions

This review study concludes that opium and its derivates such as morphine and noscapine increase cellular apoptosis and provoke angiogenesis through various mechanisms and can disrupt an organ's normal function, especially in the brain and gastrointestinal system.

Authors' contribution

All authors had an equal contribution.

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Conflict of interest

All authors declare that there is not any kind of conflict of interest.

Ethical statement

Not applicable.

Data availability

Information, data, and photos will be provided on request.

Abbreviations

CASP3	Caspase 3COX-2 Cyclooxygenase 2
CRP	C-reactive protein
cyt-c	Cytochrome c
DAMGO	D-Ala, N-MePhe, Gly-Ol-enkephalin
FADD	Fas-associated protein with death domain
GnRH	Gonadotropin-releasing hormone
hnRNA	Heterogeneous nuclear RNA
IFN-γ	Interferon-gamma
IL	Interleukin
LLCs	Lewis lung carcinoma cells
PARP	Poly ADP ribose polymerase
PDGF	Platelet-derived growth factor
PGE2	Prostaglandin E2
PSA	Prostate-specific antigen
TGF-β1	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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