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Mechanism and Target Spot of Burn and Burn Treatment Based on Network Pharmacology

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Abstract: Burn and scald is a local or systemic acute injury disease caused by various reasons acting on human body and a common disease in daily life. Network pharmacology is a new research strategy to reveal the mechanism of drug therapy and potential targets of diseases from the system level based on the network point of view.The theory of neuroendocrine-immune network (NEI) holds that there are cross reactions among nerve medium, endocrine hormone and immune active substances in the immune system to form channels for mutual regulation among the three systems, thus maintaining the body's steady state and normal physiological functions on the overall level. This article takes neuroendocrine immunity as the main line to analyze and summarize the therapeutic mechanism and mechanism of burns and scalds from different aspects. With the help of network pharmacology, the potential targets of burns and scalds are systematically screened and discussed as a whole, and the target changes involved in the mechanism of action are combined with the targets mined by network pharmacology, so as to provide theoretical and clinical basis for clinical diagnosis, treatment and new prescriptions.

1. Introduction

Burns and scalds refers to damages to skin, mucous membrane and even deep tissues caused by chemical corrosive agents, heat sources, electricity, radioactive substances, etc. They are one of extremely complicated trauma diseases and are characterized by universality, multiple and easy infection [1]. According to statistics, the annual incidence of burns and scalds in China is about 1.5% ~ 2%, and it occurs in all age groups, especially in minor children [2]. The repair of burn and scald mainly includes four stages: inflammatory reaction stage, cell proliferation stage, connectivetissue stage and wound contraction and remodeling stage. The repair mechanism is Complicated, in which burn and scald have great influence on immune system, cytokines, enzymes, etc. At present, the drugs for treating burns and scalds clinically are mainly for external use, which have the functions of resisting infection, promoting blood circulation and removing blood stasis, protecting facial injured tissues, relieving pain, reducing exudation, promoting the shedding of liquefied necrotic tissues and promoting their regeneration and repair [3].

Network pharmacology refers to the integration of drug action network and biological network, analysis of drug interactions with specific nodes or modules in this network, and can be used for the construction of drugs, diseases and drug-disease networks. At present, the principle of " one gene, one disease, one drug" may not be applicable in clinical treatment and drug development, while network pharmacology emphasizes the principles of integrity and systematicness, multi-target and multi-channel

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drug administration, observing the intervention and influence of drugs on diseases from the network level, and revealing the mystery of the synergistic effect of complex drugs on human body [4].

2. Therapeutic mechanism

Burns and scalds is one of the most common and extremely complicated trauma diseases in daily work and life. The wound healing process is also a complex biological process, including inflammatory reaction stage, cell proliferation stage, connectivetissue stage and wound contraction and remodeling stage. The four stages not only intersect and overlap with each other, but also involve the joint participation of various repair cells, inflammatory mediators, growth factors and extracellular matrix components for orderly treatment.

2.1 Inhibit inflammatory reaction, reduce tissue edema and promote wound healing

Inflammatory reaction is the basic reaction when tissue injury or pathogenic factors invade the body, and it is also the initial link of injury repair. Inflammatory factors secreted by T lymphocytes, mast cells and macrophages have a great influence on the immune system of the body, and the immune system plays a greater role in the four stages of burn and scald repair . Studies have found that at low concentrations, tumor necrosis factor-α (TNF - α) and interleukin -1(IL-1) participate in immune regulation, which can enhance the phagocytosis and sterilization of leukocytes by promoting the formation and secretion of antibodies, thus achieving the effect of enhancing immunity. However, high concentrations of TNF-α, IL-1, IL-8, etc. are endogenous heat sources, which can cause the body to overreact, cause necrosis of damaged tissues, repair cell hyperproliferation, scar hyperproliferation, etc., and induce systemic inflammatory response. At this time, drugs are needed to inhibit the inflammatory response.

2.2 Promote secretion and release of growth factors and accelerate wound healing

Wound healing is a complex and orderly biological process. It is a process in which the body repairs various tissue injuries through regeneration, repair and other means to restore the tissue structure and functional integrity of the body. Growth factor is a kind of protein that plays an important regulatory role in wound repair process. It is mainly produced and secreted by repair cells, inflammatory cells, platelets, etc. It can promote cell growth and proliferation, regulate the whole process of wound repair, and can affect wound healing. Studies have shown that epidermal growth factor (EGF), basic fibroblast growth factor (b FGF), vascular endothelial growth factor (VEGF), transforming growth factor -β(TGF-β) and platelet-derived growth factor (PDGF) have great influence on promoting wound healing. Many studies have shown that TGF-β and its signaling pathway play a key role in wound repair and scar formation. Other studies have shown that after TGF-β pretreatment, activation of p38 and p44/p42 MAPK can be detected in human hematopoietic cells and rat vascular tissues, and TGF-β is presumed to participate in vascular growth and construction through p38 mediated pathway under inflammatory conditions. P38 is one of the four categories of MAPK family. The resting state of p38 is mainly distributed in the cytoplasm. Various extracellular signals such as oxidative stress, cytokines and ultraviolet stimulation can stimulate upstream factors of p38. After activation, p38 is transferred into the nucleus, and transcription and expression of effector genes are regulated by phosphorylated transcription factors of cascade reaction. Other studies have shown that inhibiting the expression of p38 protein can improve burn shock.

2.3 Regulation of collagen synthesis and metabolism to accelerate wound healing

Wound repair is a process in which fibroblasts proliferate and produce a large amount of connective tissue formed by collagen. In the process of wound healing, fibroblasts migrate, proliferate and secrete a large amount of collagen fibers and matrix components to form granulation tissue together with newborn capillaries, repair tissue defects, create conditions for epidermal cell coverage, and increase transforming growth factor β and vascular endothelial growth factor at the same time. Collagen is an evaluation index for wound repair, of which type I and type III collagen are the most abundant. An

increase in the ratio of type Ⅲ / Ⅰ collagen indicates an increase in new collagen in collagen and promotes wound healing. Hydroxyproline is a unique amino acid in collagen. Studies have shown that collagen synthesis can be increased by affecting hydroxyproline level, thus shortening wound healing time.

3. Targets for burn and burn based on network pharmacology

Intracellular genes and proteins affect the functions of biological systems through interacting networks in groups, and burns and scalds do not heal through a single process of treatment, but show a high degree of orderliness, integrity and network therapy under the control of the body [5]. Network pharmacology is a new strategy to reveal the mechanism of drug therapy and potential targets of diseases from the system level based on the network point of view, and to express and analyze the research objects using complex network models. In this paper, the main targets related to the disease are represented in the form of fig. 1 by means of network pharmacology research methods.

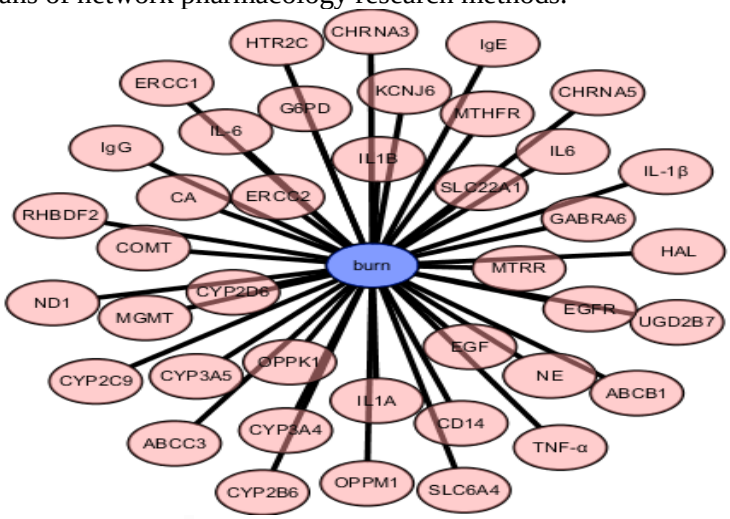


Figure 1. Target Network Map of Burn and Burn

3.1 Neuro - endocrine - immune targets

The theory of neuroendocrine immune network (NEI) [6] proposed that the three major systems of nerve, endocrine and immunity, in addition to their respective strict and fine regulation mechanisms, also jointly assume the important role of controlling the basic life activities in the body. Through mutual stimulation and restriction, they form a dynamic equilibrium network at the cellular, molecular and gene levels to achieve self-regulation and relative stability within the system. NEI networkis composed of neuroendocrine and neuroimmune systems. Neuroendocrine system regulates the immune system by combining neurotransmitters, neuropeptides, hormones, etc. with corresponding receptors in immune tissues and organs, while immune system realizes feedback regulation of neuroendocrine by bioactive factors (such as TNF-α, IL-1, IL-6) generated by immune response reaction. Burns and scalds are a kind of disease with the main clinical characteristics of body surface tissue damage and even injury to subcutaneous tissue, muscle, bone, joint, nerve, blood vessel and viscera. Now we can improve the treatment of burn and scald by predicting potential neuro - endocrine - immune targets.

Through analysis above, the treatment of burn and scald requires multi - channel, multi-target and multi-level comprehensive regulation to achieve wound repair and healing. A series of inflammatory reactions occur under the action of the autoimmune system in the early stage of the patient. T lymphocytes and macrophages remove damaged tissues and foreign bodies at the wound surface by secreting inflammatory factors and resist bacteria or viruses. However, excessive inflammatory factors can cause burn and scald wounds to continue to deepen and necrosis. Therefore, anti-inflammatory effects can be achieved by regulating proinflammatory factors (TNF-α, IL-1β, IL-6, IL-8) and anti-inflammatory factors (IL-4, IL-10) [7]. Endoplasmic reticulum stress exists in skeletal muscle

after severe burns, and the increase of Ca 2 + content in cytosol of skeletal muscle cells causes the increase of calpain content and activity. Calpain is a kind of calcium-dependent protease, which is involved in many physiological processes such as protein degradation, apoptosis, cytoskeleton formation and cell cycle cycle after activation. However, severe burns will cause excessive activation of calpain, which will hydrolyze various cytoskeletal proteins, change the normal physiological function of cells, and cause tissue damage. After tissue injury, monocytes synthesize and secrete a variety of growth factors. EGF is a polypeptide substance that can stimulate the proliferation of epidermal keratinocytes and fibroblasts, promote the formation of new blood vessels and the synthesis of nucleic acid proteins. After severe burns, NE rises, and the body experiences severe stress reactions, which are mainly manifested by a series of neuroendocrine reactions with hypothalamus-pituitary-adrenal axis (HPA) excitation as the main component, resulting in increased vascular permeability, large amount of body fluid extravasation, and brain edema induced by increased VEGF expression in brain tissue. Skin, which contains drug metabolizing enzymes and sweat glands, is the largest organ of human body and plays an important role in biotransformation, detoxification and elimination of abnormal biomass and endogenous toxicants. Studies have found that no mRNA (catechol -O- methyltransferase COMT, nicotinamide N- methyltransferase, aldehyde oxidase, etc.) of enzymes related to detoxification has been detected in the skin of burned rats. ROS production is out of balance with the overall antioxidant capacity of the body, which causes permanent loss of the biotransformation and excretion functions of the skin at the burn site, causing oxidative stress and insulin resistance.

3.2 Other target spots

Extensive skin injury and tissue damage in patients with extensive burns are often accompanied by a large amount of tissue fluid exudation, varying degrees of water and electrolyte disorders and organ dysfunction or failure, leading to a decline in the body's tolerance to anesthesia, which is more prone to anesthesia accidents and even death of patients. Genes can lead to individual differences in drug effects and drug metabolism. Most of fentanyl, an analgesic opioid receptor agonist, is metabolized by liver, and the polymorphism of CYP3A4 enzyme in liver seriously affects fentanyl metabolism. CYP3A4 enzyme is determined by CYP3A4 gene. CYP3A4 gene is located on the long arm of chromosome 7, including 13 exons and 12 introns, with 40 alleles, among which CYP3A4* 1G gene mutation is proved to have functional significance. CYP3A4 enzyme activity is monomorphic distribution, and changes in its in vivo content or activity can cause changes in drug metabolism kinetics or pharmacodynamics, thus resulting in individual differences. Therefore, it is necessary to determine the dosage according to the individual differences of patients, so as to increase the effectiveness and persistence of anesthesia and analgesia for postoperative patients and reduce adverse reactions.

4. Discussion

Burns and scalds are one of the most common traumatic diseases, especially among children, teenagers and the elderly [8]. Nerve - endocrine - immune network (NEI) is one of the attractive research fields in recent years. It maintains the body's steady state and normal physiological function on the overall level [9,10]. At present, although in-depth and extensive research has been carried out on the mechanism of action and mechanism for treating burns and scalds, effective means for regulating NEI network have not been found.

Through analysis, it is found that the therapeutic targets for burns and scalds from the perspective of network pharmacology are highly consistent with the therapeutic mechanism of the disease, all of which are aimed at regulating proinflammatory factors (TNF-α, IL-1β, IL-6, IL-8) and anti-inflammatory factors (IL-4, IL-10) to reduce inflammation and infection, and secreting growth factors (such as EGF) to promote wound healing, indicating that the targets screened by network pharmacology can be used as the first choice for disease treatment.Studies have found that abnormalities of neurotransmitters or cytokines such as nerves, endocrine and immunity participate in the development of burns and scalds, and abnormalities of the network system penetrate through the treatment mechanism of burns and scalds. Based on network pharmacology, this paper analyzes the regulatory effect of NEI on burn and scald

diseases, and finds several potential therapeutic targets for burn and scald. It reveals the potential role and broad application prospect of network pharmacology in the treatment and regulation of burns and scalds, provides ideas for in-depth discussion of the therapeutic targets of network pharmacology for burns and scalds, and lays a foundation for clinical treatment of burns and scalds and the therapeutic mechanism.

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