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Effect and Significance of Different Sources of Exosomal MicroRNA on the Progression of Liver Fibrosis

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Abstract

Hepatic fibrosis (HF) is a pathological condition characterized by over-extracellular matrix (ECM) aggregation and angiogenesis, which easily leads to cirrhosis and hepatocellular carcinoma. Currently, there is no specific drug therapy strategy for this pathological change. More and more evidence shows that microRNAs (miRNAs) carried by exosomes are involved in the early fibrosis process of liver by mediating intercellular communication, and they can be used as potential biomarkers and therapeutic targets for early HF. In this review, we discussed the hepatogenic, stem cell line and worm-derived exosomes according to the main types of exosomes, and summarized in detail the biological functions of coated miRNA and their multi-dimensional roles in hepatic stellate cell activation, ECM deposition, inflammatory infiltration and liver fibrosis. This provides a new way to diagnose, improve and even reverse HF with miRNA in clinical practice.

Keywords: Hepatic Fibrosis, MicroRNA, Biomarkers, Liver Fibrosis, Chronic Liver Disease, Cirrhosis, Hepatic Stellate Cells (HSCs), Liver Inflammation, Extracellular Matrix (ECM), Collagen Deposition, Fibrogenesis, Hepatocellular Carcinoma (HCC), Alcoholic Liver Disease.

Introduction

Hepatic fibrosis (HF) is a common pathological feature shared by most chronic liver diseases, including viral hepatitis, alcoholic liver disease, and cholestatic liver disease. This process represents a wound-healing response of the liver to long-term chronic injury [1,2].

Upon sustained chronic damage, liver cells undergo degeneration and necrosis, accompanied by massive infiltration of immune cells, such as macrophages, neutrophils, and lymphocytes, which produce various inflammatory mediators. As the inflammatory response persists, hepatic stellate cells (HSCs) are activated into a myofibroblast-like phenotype, leading to the excessive deposition of the extracellular matrix (ECM) and the aberrant proliferation of connective tissue in multiple regions of the liver. The excessive ECM deposition and subsequent tissue remodeling result in structural abnormalities, forming fibrotic nodules that can progress to cirrhosis and even hepatocellular carcinoma (HCC) [3,4].

In recent years, with the deepening research into the mechanisms of HF, the critical role of dysregulated intercellular communication in its onset and progression has been increasingly recognized. In particular, the unique biological function of exosomes in mediating cell-to-cell information transfer has garnered widespread attention. Exosomes are extracellular vesicles with a diameter of approximately 40–160 nm (average size around 100 nm). They encapsulate various biologically active substances, including growth factors, metabolic enzymes, mRNA, microRNAs (miRNAs), and specific proteins. Due to their topological similarity to cells, exosomes can exert regulatory effects by binding to receptors on target cells or by direct endocytosis.

MiRNAs, small non-coding RNA clusters 18–25 nucleotides in length, regulate gene expression by binding to target mRNAs, thereby influencing cell proliferation, apoptosis, and differentiation [5-7].

A growing body of research suggests that exosomal miRNAs play a crucial role in the progression of HF. The stability of exosome-encapsulated miRNAs in bodily fluids such as blood makes them advantageous for HF diagnosis. Moreover, the aberrant expression patterns of specific miRNAs in hepatic fibrosis offer new perspectives for anti-fibrotic therapeutic strategies, positioning them as potential therapeutic targets [8,9].

Therefore, this review aims to comprehensively summarize the mechanisms of exosomal miRNAs from different sources in HF, and to explore their prospects in diagnosis and treatment, which holds significant importance for improving and potentially reversing the progression of HF in patients.

Exosomal MicroRNAs from Different Sources and Hepatic Fibrosis

Hepar-Derived Exosomal MicroRNAs and Hepatic Fibrosis

The hepatic, as the largest solid organ in the human body, is crucial for maintaining glucose homeostasis, synthesizing plasma proteins, nutrient metabolism, and possesses a unique regenerative capacity. It is composed of various types of cells, including hepatocytes, liver sinusoidal endothelial cells (LSECs), resident macrophage Kupffer cells (KCs), hepatic stellate cells (HSCs), and biliary epithelial cells (BECs) [10].

HSCs can interact with a variety of cells in the liver due to their special anatomical location in the Disse space. The activation and proliferation of hepatic stellate cells (HSCs) is considered as a key event in the pathogenesis of hepatic fibrosis. Multiple liver cell types, such as hepatocytes, KCs, and cholangiocytes, can directly influence the degree of HSC activation and thus regulate the progression of HF by secreting and up taking exosomes [11, 12].

Crucially, miRNAs, as important components encapsulated within exosomes, participate in regulating the physiological and pathological functions of the liver and are closely associated with liver injury, metabolic imbalance, and hepatic fibrosis. Specifically, exosomal miRNAs originating from different hepatic cell types can modulate the activation status of HSCs, thereby impacting the development and progression of liver diseases.

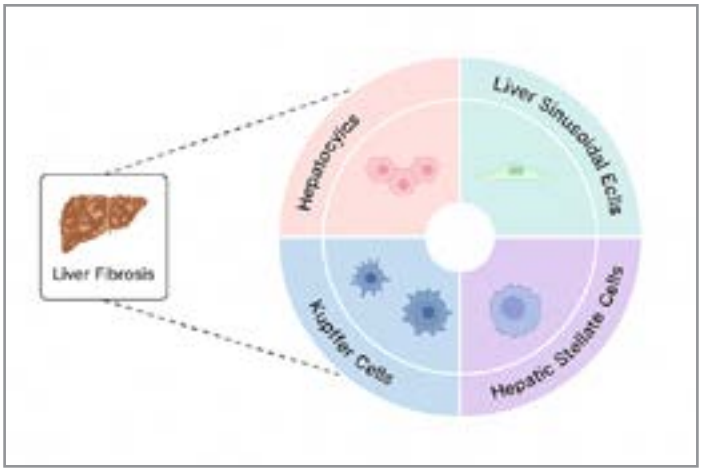

Figure 1: Liver Derived cells Leading to Cirrhosis

Exosomal MicroRNAs from Hepatocytes and Hepatic Fibrosis

Hepatocytes are the most abundant parenchymal cells in the liver, accounting for approximately 90% of the total cell population, and serve as the primary cells for regeneration upon inflammatory stimuli. Increasing evidence demonstrated that exosomes, the small extracellular vesicles (EVs) released by almost all types of cells, including hepatocytes and cholangiocytes in the livers, play a critical role in cell-to-cell communication under normal and pathological conditions .

Research indicates that normal hepatocytes secrete exosomes containing miR-21-5p, which targets and silences the Smad7 gene, thereby achieving an inhibitory effect on HF. Similarly, found that exosomes secreted by normal hepatocytes treated with rhodioloside exhibited a significant increase in miR-146a-5p content. This miRNA inhibits the expression of the EIF5A2 gene, leading to the blockage of epithelial-mesenchymal transition (EMT) and the inactivation of HSCs, ultimately contributing to the anti-fibrotic effect of rhodioloside [13].

Conversely, it is more commonly observed that damaged hepatocytes secrete exosomes containing different miRNAs, which promote the onset and progression of HF. For instance, miRNAs in EVs released from lipotoxic hepatocytes (miR-128-3p is most effective) suppress PPARgamma expression in HSC, leading to significantly upregulated expression of fibrotic genes, including Col1a1 and Atca1 [14].

Furthermore, viral hepatitis is a major cause of hepatic fibrosis. When hepatocytes are subjected to viral attack, they release exosomes carrying small molecules like miRNAs to HSCs, inducing their activation and resulting in fibrosis. For example, after hepatitis B virus (HBV) infection, damaged hepatocytes release exosomes containing miR-222, which inhibits the transferrin receptor to suppress ferroptosis, thereby contributing to HF. Similarly, when hepatocytes are infected with hepatitis C virus (HCV), they secrete exosomes with miR-19a, which promotes HSC activation by targeting SOCS3 to activate the STAT3-mediated TGF-β1 signaling pathway [15,16].

In summary, hepatocytes in a normal or therapeutic-drug-treated state can transmit specific miRNAs via exosomes to block HSC activation pathways, thus slowing down or inhibiting the progression of HF. Conversely, under continuous pathogenic interference, hepatocytes utilize exosomal miRNAs to regulate the expression of corresponding target genes, leading to increased expression of fibrotic markers, excessive ECM deposition, and HSC activation, thereby accelerating the fibrotic process. From the perspective of clinical application potential, current research is predominantly focused on the microenvironmental changes in HF under pathological conditions.

However, the self-defense mechanisms of normal hepatocytes in response to external disturbances, particularly those regulated by exosomal miRNAs, remain insufficiently explored. Deeper future research in this area may offer novel insights for the prevention and early intervention of hepatic fibrosis.

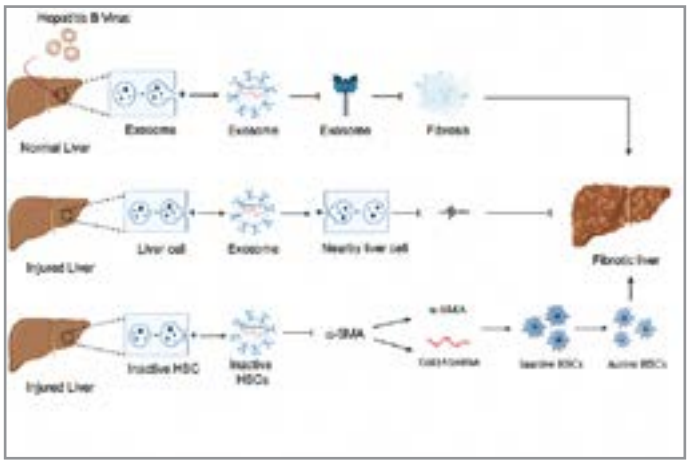

Figure 2: Mechanism of miRNA Mediated Liver Fibrosis in Hepatocyte Exosomes

Exosomal MicroRNAs from Hepatic Stellate Cells (HSCs) and Hepatic Fibrosis

HSCs are resident non-parenchymal perisinusoidal cells in the liver, serving as the primary collagen-producing cells. Their activation is considered a crucial factor in hepatic fibrosis. A critical event during fibrosis is HSC activation, in which HSCs transform from a quiescent, vitamin A rich state to a proliferative, contractile, myofibroblast-like state. Activation of HSCs is driven by a variety of mediators, such as reactive oxygen species, chemokines, growth factors, matrix hardness, stromal cell proteins, and injury-related molecular patterns, which are also secreted by adjacent cells and signal HSC scar formation in an autosecretory and/or paracrine manner [17-19].

Research suggests that HSC-secreted exosomes carrying miR-199a-5p target the SIRT1 gene, promoting the proliferation and activation of LX-2 cells in vitro and accelerating the progression of HF in BDL rats [20].

However, Li Chen et al. reported a contrasting finding: the overexpression of miR-199a-5p in HSCs targeted and inhibited cellular communication network factor 2 (CCN2). This resulted in the low-level expression of fibrotic genes in quiescent HSCs and, to a certain extent, suppressed HSC activation. These studies collectively indicate that miR-199a-5p may exhibit diametrically opposed biological functions under different research contexts, reflecting the complexity and diversity of its role [21].

Moreover, LX-2 cells could rapidly shuttle exosomal MiR-214 to hepatocytes that suppressed connective tissue growth factor (CCN2) 3'-UTR activity and expression of CCN2 and its downstream targets such as alpha-SMA and collagen, inhibiting fibrogenic signaling [22].

In summary, exosomes secreted by HSCs play a critical role in the progression of hepatic fibrosis, with miRNAs being key regulatory factors within them. miR-199a-5p and miR-214 regulate HSC activation through different signaling pathways, reflecting the versatility and complexity of these miRNAs under varying environmental conditions. In future research, further exploration of the mechanisms of these miRNAs under different pathological conditions will be key to achieving precise diagnosis and personalized treatment for hepatic fibrosis. Furthermore, these studies also alert us that when developing miRNA-targeted therapeutic strategies, their diversified functions and potential side effects must be considered to ensure both efficacy and safety.

Exosomal MicroRNAs from Liver Sinusoidal Endothelial Cells (LSECs) and Hepatic Fibrosis

Liver sinusoidal endothelial cells (LSECs) are specialized vascular endothelial cells in the liver, lining the inner walls of the sinusoids. They account for approximately 50% of the liver's non-parenchymal cell population and are typically the first liver cell type to respond when liver injury occurs. LSECs are unique in that they possess fenestrations (pores) and lack a basement membrane, allowing blood plasma components to pass through while retaining blood cells [23, 24].

LSECs secrete exosomes that express high amounts of Sphingosine kinase 1 (SphK1), which promote HSC migration by triggering AKT phosphorylation [25]. These exosomes enter HSCs via a fibronectin-integrin dependent pathway, activating the phosphorylation of the Protein Kinase B (Akt) pathway, which in turn promotes HSC migration and activation. Furthermore, these exosomes have been implicated in HSC activation in BDL or CCl4-induced fibrosis models, suggesting that LSEC exosomes may act as a mediator of HSC activation in the progression of HF. For example, miR-128-3p released by both hepatocytes and

LSECs is effectively internalized by HSCs during lipotoxicity, thereby promoting PPAR-γ mediated hepatic fibrosis [25].

Despite the proven crucial regulatory roles of miRNAs in exosomes derived from other liver cell types, such as hepatocytes and HSCs, the specific mechanisms of miRNA-containing exosomes secreted by LSECs remain to be fully elucidated. Therefore, future research focusing on exosomal miRNAs within LSECs may unveil novel regulatory mechanisms and provide potential molecular targets for anti-fibrotic therapies.

Exosomal MicroRNAs from Hepatic Macrophages and Hepatic Fibrosis

Macrophages, which include circulating monocyte-derived macrophages and resident Kupffer cells (KCs), exhibit high plasticity. Based on signals from the liver microenvironment, macrophages can polarize into either the M1 phenotype (classically activated) or the M2 phenotype (alternatively activated), thereby participating in the outcome of chronic liver injury . Notably, due to their different polarization directions, these two macrophage phenotypes exert opposite effects on inflammation regulation and HF progression. M1 macrophages secrete pro-inflammatory factors, promoting the body's inflammatory response, while M2 macrophages release anti-inflammatory factors, exerting the opposite effect to M1 cells. Sun et al. suggest that whether the HF process accelerates or is inhibited depends on the imbalance bias between M1/M2 macrophages: a predominance of M1 macrophages generally indicates HF progression, whereas a shift toward M2 is often associated with the improvement of liver fibrosis [26-30].

A growing number of experiments have demonstrated the role of exosomal miRNAs in hepatic fibrosis. Lishan Chen et al. found that exosomes secreted by THP-1 cells, when stimulated by lipopolysaccharide (LPS), carry miR-103-3p. This miRNA targets and reduces the expression of the zinc finger transcription factor KLF4, thereby interfering with its binding to Samd2/3 and the α-SMA promoter, increasing the expression of α-SMA, promoting the proliferation and activation of HSCs, and accelerating the HF process.

Conversely, anti-fibrotic effects can be achieved by inhibiting M1 polarization or promoting M2 polarization. Forsythiaside (an active component of the traditional Chinese medicine Forsythia suspense) can inhibit M1 macrophage polarization and suppress the secretion of exosomes rich in miR-125b-5p, thereby blocking the JAK1/JAK2-STAT-1 and Notch1 signaling pathways to inhibit HF progression. Mengying Hu et al. discovered that liver macrophages expressing the relaxin receptor, after binding with relaxin, transform their phenotype from M1 to M2 and release exosomes containing miR-30a-5p, which inhibits HSC activation [31, 32].

However, the notion that M2 polarization always improves the HF process is not absolute. Research has shown that during arsenic poisoning, exosomal miR-21 can induce M2 polarization of macrophages, which subsequently activates HSCs, leading to hepatic fibrosis. Similarly, in HCV infection, the virus induces M2 polarization of macrophages, activating HSCs and promoting HF progression [33].

In conclusion, the regulation of macrophage polarization and associated exosomal miRNAs is complex and dualistic. The direction of macrophage polarization and its influence on HF progression vary significantly across different liver microenvironments. More in-depth research is still required to fully elucidate the specific roles of macrophages in the HF process.

Exosomal MicroRNAs from Stem Cell Lines and Hepatic Fibrosis

Mesenchymal Stem Cells (MSCs) are a type of multipotent stem cell characterized by self-renewal, multi-lineage differentiation, and immunomodulatory properties, and they are widely distributed in tissues such as bone marrow, umbilical cord, and adipose tissue. Relevant studies indicate that MSC-derived exosomes possess tissue repair and immunomodulatory functions similar to those of MSCs themselves, and they play a vital role in hepatic fibrosis by delivering various types of miRNAs to target cells [34-38].

Jing Ma et al. reported that exosomes derived from bone marrow mesenchymal stem cells (BMSCs) carry circCDK13, which targets miR-17-5p to regulate the expression level of MFGE8, thereby inhibiting HF. Similarly, miR-618 targeting the Smad4 gene and miR-192-5p targeting PPP2R3A , both delivered by BMSC-derived exosomes, can inhibit the viability of HSCs, leading to a reduction in the expression of fibrotic markers and the extent of HF [39-41].

Fang Cheng et al. demonstrated that miR-27b-3p derived from human umbilical cord mesenchymal stem cells (UCMSCs) alleviates hepatic fibrosis by downregulating the YAP/LOXL2 signaling pathway in HSCs. Furthermore, UCMSC-derived exosomes containing miR-148a regulate the HF process by influencing the pro-inflammatory/anti-inflammatory properties of macrophages. Specifically, miR-148a reduces the expression level of KLF6, a pro-inflammatory transcription factor, thereby inhibiting pro-inflammatory (M1) macrophages and simultaneously promoting anti-inflammatory (M2) macrophages by inhibiting the STAT3 pathway. The reduction in KLF6 expression leads to the downregulation of M1-macrophage-specific marker genes, while the effect on M2-macrophage markers is the opposite [42, 43].

Thus, a profound and complex cellular communication exists between MSC exosomes from different tissues and the constituent cells within the HF microenvironment, often initiating tissue repair functions in response to damaged hepatocytes. MSCs demonstrate immense potential and promising application prospects for improving hepatic fibrosis, potentially offering an effective and novel therapeutic approach for HF patients. However, the anti-fibrotic mechanisms are currently not fully elucidated, and their application in clinical practice awaits further validation.

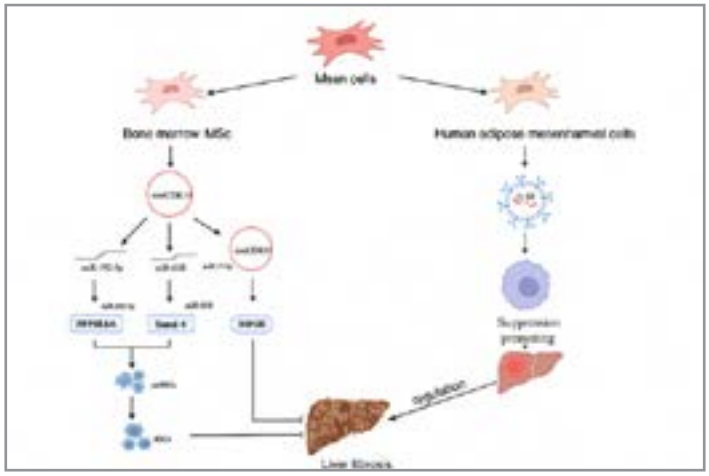

Figure 3: Mechanism of miRNA Mediated Liver Fibrosis in Stem Cell Line Exosomes

Exosomal MicroRNAs from Parasite Sources and Hepatic Fibrosis

According to the World Health Organization, infectious diseases pose a great threat to human health, accounting for about 17% of all deaths in the world in 2020 (out of 9.2 million deaths). Vector-borne diseases, including tick-borne diseases caused by pathogens such as bacteria and viruses and parasites such as Babesia divergens, B. microti, and B. venatorum, are an emerging global health issue Hepatic parasites are those that reside, develop, and obtain nutrition within the liver or biliary system. These include various species of flukes, protozoa, nematodes, and echinococcus, some of which can permanently reside in the liver, such as Echinococcus and Schistosoma [44].

Upon host infection, various parasite-derived molecules secreted by these pathogens act as initiating factors, stimulating liver cells to recruit massive numbers of immune cells (macrophages, neutrophils, lymphocytes, etc.) to the vicinity of the ova or larvae, causing inflammatory infiltration and inducing a granulomatous reaction. As the host attempts to kill the ova or larvae, the granuloma undergoes fibrosis, leading to liver damage and other hepatic diseases.

With continuous research, parasite-derived exosomes can carry a large amount of parasite miRNA, which is involved in the interaction between the parasite and the host, and play a vital role in parasite invasion and infection, pathogenesis, and immune evasion. Furthermore, the miRNAs carried by these exosomes, once internalized by host liver cells, regulate corresponding target genes to influence the HF process. Since different parasites, or the same parasite at different developmental stages, secrete distinct exosomes, the molecular mechanisms through which they regulate HF progression naturally vary, which will be discussed in the following sub-sections [45, 46].

Exosomal MicroRNAs from Schistosoma Sources and Hepatic Fibrosis

It has been reported that 79 and 225 mature miRNAs have been identified in Schistosoma japonicum and Schistosoma mansoni, respectively, with 12 of them being schistosome-specific. Pro-fibrotic miRNAs originating from schistosome ova (eggs) are packaged in exosomes and transported to the liver, where they accelerate the onset and progression of HF [47].

For instance, S. japonicum ova release exosomes containing sja-miR-2162. After being internalized by HSCs, this miRNA targets TGFBR-3, promoting the transition of HSCs from a quiescent to an activated state, leading to the excessive accumulation of ECM components and inducing HF. This process is associated with the canonical TGF-β signaling pathway [48].

Conversely, some schistosome-derived miRNAs exhibit inhibitory effects. sja-miR-71a directly targets Semaphorin 4D (Sema4D) to inhibit the TGF-β1/SMAD and IL-13/STAT6 pathways, thereby mitigating the pathological damage caused by the parasitic infection [49].

Furthermore, research by Haoran Zhong et al. demonstrated that sja-let-7, derived from the worm stage of S. japonicum, participates in HSC activation by targeting Col1α2 and downregulating the TGF-β/Smad signaling pathway. It is thus evident that Schistosoma releases exosomes with varied contents at different developmental stages, which can either promote or inhibit the onset and progression of HF. More in-depth and meticulous research is warranted to fully explore these mechanisms [50].

Hepatic Fibrosis and Exosomal miRNAs Derived from Clonorchis sinensis

Unlike schistosomiasis, chronic hepatic injury caused by Clonorchis sinensis (the Chinese liver fluke) is primarily attributed to high parasitic burden. During C. sinensis infection, the sustained presence of chronic inflammation and extracellular matrix (ECM) accumulation in the hepatic microenvironment leads to hepatic fibrosis (HF), resulting in continuous hepatic damage. Similarly, C. sinensis can deliver miRNAs to host cells, thereby regulating inflammatory responses and intervening in the HF progression [51, 52].

Specifically, Csi-let-7a-5p, secreted by adult C. sinensis, is transported to macrophages. It targets the Socs1 and Clec7a genes, subsequently utilizing the NF-κB signaling pathway to polarize the macrophages into the M1 phenotype. However, the specific mechanisms by which these miRNAs contribute to parasite-induced hepatic fibrosis still require further investigation [53].

Future Perspectives

A vast number of miRNAs originating from diverse cell types—including various hepatic cells (hepatocytes, hepatic stellate

cells, hepatic sinusoidal endothelial cells, and macrophages), stem cell lines, and parasites—are implicated in the regulation of hepatic fibrosis (HF). The dysregulation of these miRNAs leads to altered expression of their target genes, thereby influencing the progression of HF [54].

Furthermore, liquid biopsy techniques, which have been refined based on the high specificity and sensitivity of certain miRNAs, await further clinical exploration. Although no miRNA-based drugs have reached the market yet, research focusing on using miRNAs for drug delivery and targeting specific cells to alter their function is progressively moving toward clinical practice.

Undeniably, this demanding approach requires researchers to master the ability to analyze, identify, and predict exosomal content, potency, and select precise dosages to ensure effective in vivo studies, highlighting the inherent complexity. Therefore, whether focusing on the molecular mechanisms of miRNAs in the HF process or aiming at the diagnostic and therapeutic applications of miRNAs for HF, there is a persistent need for more extensive, in-depth, and well-integrated systemic research [55, 56].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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