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Angiogenic potential of YKL-40 in the dynamics of tumor niche

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ABSTRACT

A multitude of clinical studies showed the elevation of YKL-40 in subjects with different kinds of tumors. It is predicted that an inherent correlation exists between survivals of cancer patients with total YKL-40 serum levels, making this factor as a potential novel biomarker. However, the crucial role of YKL-40 in the dynamics of cancers, especially angiogenesis, has not yet been completely addressed. In this review, we highlighted the various facets of YKL-40 and its importance in cancer biology as a bio-shuttle in gene therapy.

1. Introduction

CHI3L1 named also as YKL-40, HC-gp39, and breast regression protein 39, is synthesized by the activity of YKL-40 gene. First, YKL-40 was discovered in the secretome of human osteosarcoma cell line [1]. This glycoprotein is a 40 kDa with three different amino acids such as tyrosine, lysine, and leucine located at N terminal molecular structure. YKL-40 was found to have a considerable homology (near to 53%) to a member of the family 18 chitinases, having capability to interact and catalyze chitin [2–4]. It was reported YKL-40 binds directly to chitin and fails to break down chitin due to a lack of glycosyl hydrolase activity [5]. As a matter of fact, YKL-40 is referred to as chitinase-like protein. In normal physiological conditions, Different cell types like activated neutrophils, macrophages, vascular smooth muscle cells, and chondrocytes express YKL-40 [6–9]. Its expression has been observed during early stages development of human muscle cells [10]. In contrast to normal cells, YKL-40 is known to be observed in many solid tumors like kidney, breast, small cell lung carcinoma colon, *etc.* [11–19]. The participation of YKL-40 factor has been also evidenced during extracellular matrix remodeling, macrophage-induced inflammation, and T-cell activity [4,6]. In line with this statement, it has been previously demonstrated that serum samples pooled from patients with inflammatory diseases, diabetes, and cardiovascular diseases contain large amounts of YKL-40 [20]. This glycoprotein is more likely to play a crucial role in the cells with active metabolism, and the sites where a high cell turnover occurs (during mammary involution, for example) [21]. As a result, growth stimulating property has been indicated for the YKL-40 in several cell types [4,9,21,22]. The high content of YKL-40 in patients with tumors was shown to be highly associated with a lower survival and tumor invasion, especially glioblastoma [23]. Although the real YKL-40 function in cancer dynamic is under investigation, it is assumed that YKL-40 may participate in survival/growth of the tumor cells. Considering a close relation with inflammation, YKL-40 is considered to play a role during cancer development, as it is highly secreted by tumor-associated macrophages. However, there is lack of firm evidence to confirm these suggestions.

2. Tumor vasculature: angiogenesis

Angiogenesis is a sophisticated phenomenon with the generation of new blood vessels from the preexisting vascular bed. Angiogenesis commonly occurs during embryonic development [24]. After birth under physiologic conditions, ECs are in a quiescent state and survive for hundreds of days prior to being replaced [25]. During the activation of angiogenesis signaling, the blood vessels will be destabilized. VEGF-A is well-known as angiogenic factors able to augment the formation and sprouting of blood vessels [26]. Following interaction with its main receptor VEGFR-2, VEGF promotes a signaling cascade which induces

Abbreviations: CHI3L1, Chitinase-3-like protein 1; ECs, endothelial cells; VEGF-A, vascular endothelial growth factor A; MMPs, matrix metalloproteinases; VE-cadherin, vascular endothelial cadherin; N-cadherin, neural cadherin; HMVECs, human microvascular endothelial cells; PI3K, phosphoinositide 3-kinase-protein kinase B; ER, estrogen receptor; PR, progesterone receptor; TGF, transforming growth factor; bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor

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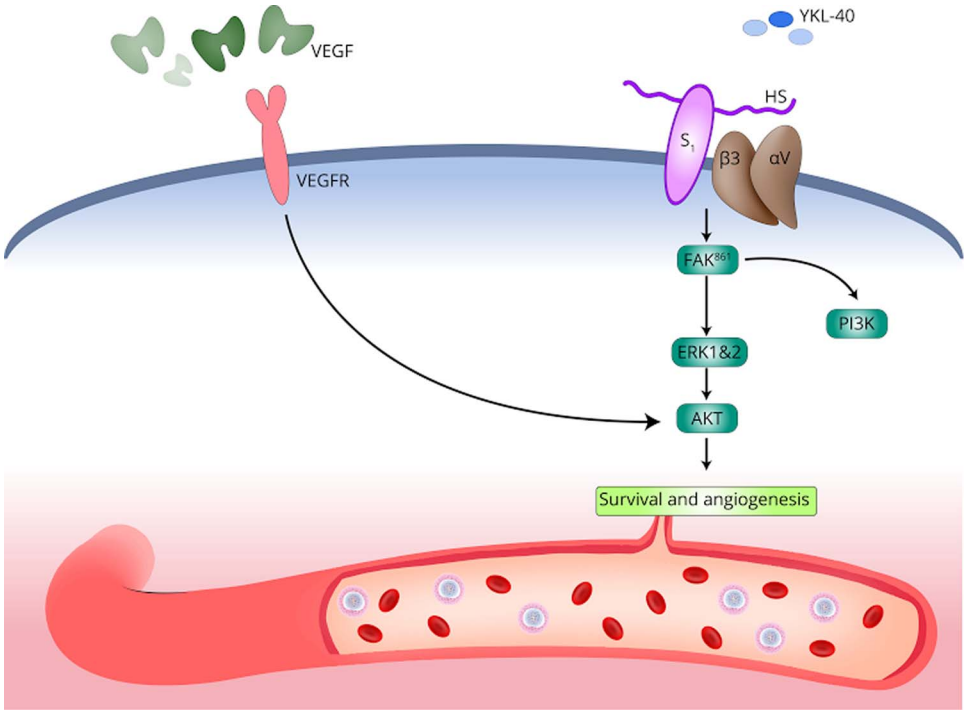

Fig. 1. YKL-40 induces the coordination of syndecan-1 (S1) and integrin αvβ3 through binding heparan sulfate chains (HS) of S1 on the cell surface. The intracellular signaling pathway includes pFAK861 and downstream MAP kinase Erk 1 and 2, leading to angiogenic responses and angiogenic gene expression as well (*e.g.*, Flk-1). Elevated Flk-1 may also sensitize angiogenic responses to VEGF. An additional PI3K-AKT pathway participating in YKL-40-induced angiogenesis in endothelial cells warrants further investigation. HS, Heparan sulfate chains; VEGF, vascular endothelial growth factor, FAK, focal adhesion kinase; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein; S1, syndecan-1; Erk, extracellular regulated kinase; AKT, Protein kinase B (PKB), also known as AKT.

the proliferation and survival of ECs (Fig. 1). Physiological angiogenesis follows a basic mechanism which is explained below [24,25,27,28]. During tumor development, an aberrant angiogenesis occurs inside tumor mass which is known as cancer angiogenesis [29]. In this process, host vascular system is recruited to the tumor sites, leading to the generation and sprouting of new blood vessels. These sequential steps were shown to be a key step essential for tumor maintenance and progression [24,27]. Tumor angiogenesis has a high rate of similarities with normal angiogenesis, however, this process appears to be more dynamically active and neo-vascularization mostly occurs as a result of the hypoxic nature of proliferating tumor cells [26–28]. Hypoxia is thought to be an inductive factor to develop new blood vessels through a serious of mechanisms such as overproduction of VEGF, Matrix metalloproteinases (MMPs), and etc. Despite having a high rate of similarities, tumor, and normal vessels differ in a few key ways follows as. First, tumor cells are shown to be over-dilated and with a high rate of permeability than normal vessel network. Second, tumor vessels have a highly disorganized nature without a well-structured morphology. And finally, a high turnover of EC proliferation has been documented in tumor cells rather than a low-rate proliferation of normal ECs [26–28].

3. Molecular mechanisms mediating ECs junctions

ECs in collaboration with pericytes create a stable connection permitting the blood transportation through various tissues of the body. At the same time, these cell-cell junctions need to be adequately flexible to allow the body having a proper feedback to particular stresses, such as inflammatory conditions or wound healing process. Therefore, one could hypothesize that these connections must be precisely regulated via molecular mechanisms to allow the blood vessel growth and permeability [30–32]. The cellular connections in vessels contain two important junctions; endothelial-endothelial cell binding and endothelial-pericyte connection [30].

The junction between the ECs is mainly governed by certain intercellular junctions known as tight junctions and adherence junctions [33]. Using these junctions, the ECs are allowed to connect with each other, contributing to ions transport and transduce the molecular signals. The existence of special intracellular spaces allows other cells to pass from the paracellular route, such as leukocyte migration seen during inflammation [31,33,34]. A key factor in this issue is vascular endothelial cadherin (VE-cadherin) an endothelial-specific adhesion molecule, which helps to maintain and control the cell junctions. VE-cadherin is expressed in a polarized manner with a tending toward a specific end of the cells. In normal condition, when VE-cadherin is in a normal contact with an adjacent VE-cadherin molecule of another ECs is anchored in site and shows a quiescent manner [30,31,33]. These signal information are transmitted using a well-described molecular network, the cadherin/catenin complex [30,31,33]. The homophilic binding between the neighboring VE-cadherin proteins on ECs leads to stabilization of VE-cadherin interaction with 15 beta-catenin complexes. β-Catenin, in turn, interacts with alpha-catenin which is tethered to actin filaments allowing the cells to create a well-established physical contact with one another and the cytoskeleton.

During tumor angiogenesis, VEGF is highly produced by tumor cells and binds to VEGFR-2 thereby creating a link with VE-cadherin. This process comes up with a phosphorylation cascade in which VE-cadherin and beta-catenin become phosphorylated, leading to the dissociation of the complex. In normal conditions, these events cause an enhancement in vascular permeability and angiogenesis [30,31,33]. In addition to endothelial-endothelial adhesion, endothelial to pericyte junction is crucial to maintaining the stability and permeability of vessel. For this propose, the cell adhesion molecule neural cadherin (N-cadherin) play the key role [33,35]. The expression of N-cadherin is reported in neuronal lineage, pericytes, cancer cells, and ECs [32,36]. Regarding mechanistically events, N-cadherin behaves in the same way in terms of the ability to interact with beta-catenin, and in the cases of phosphorylation or cleavage, the complex dissociates. Despite VE-cadherin, N-cadherin is not tending to localize to the adherens junctions; however, it is expressed throughout the membrane [31,32]. Thus, it provides accessible areas on the membrane, allowing the pericytes to bind and maintain the vessels and to regulate permeability [36,37].

4. Role of YKL-40 in angiogenesis

It is known that YKL-40 expression plays an essential role in tumor growth via accelerating angiogenesis [38–40]. YKL-40 was also