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Is survivin a novel pathway for the treatment and pathogenesis of keloid?

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ABSTRACT

Keloids behave like benign tumors as they grow beyond the boundaries of the original wound margin, do not regress spontaneously, and recur despite treatments. Recently, accumulating evidences showed that survivin played an important role in cell growth, apoptotic resistance, and cell cycle control. More than that, survivin was confirmed to be associated with tumor angiogenesis and chemoresistance. Survivin blocker therapy has been proved to be a novel treatment in some kinds of tumors. Our preliminary work showed that survivin expression was significantly higher in keloids than in normal skin. The mRNA and protein levels of survivin were downregulated in keloid fibroblasts by survivin-siRNA. Therefore, we hypothesize that survivin has a profound effect on keloid formation and progression. Therefore, survivin may be a potential therapeutic target for keloids. Our hypothesis sheds light for the first time on the role of survivin involves in keloid pathophysiology and provides with novel therapeutic implications for keloids that are associated with apoptosis.

Introduction

Keloids are pathologic scars that continue to grow aberrantly beyond the original boundary of cutaneous injury. Keloids behave clinically as benign tumors, growing locally beyond their original margins. This observation has led to the suggestion that keloids are a neoplastic disease. By causing pruritus, pain and contractures, keloids can dramatically affect a patient's quality of life, both physically and psychologically. Numerous treatment options have been described including occlusive dressings, compression therapy, intralesional steroid injections, imiquimod cream, laser and radiation therapy, cryosurgery, 5-fluorouracil, bleomycin, and interferon therapy. Although various treatment options are available, there is no consensus as to what the optimum approach should be. Better understanding of the molecular mechanisms behind keloid development led to the development of new promising therapies. Despite relatively high prevalence of keloids in general population, the mechanisms underlying keloid formation are only partially understood [1,2].

For keloid, the genetic basis for alterations in fibroblast response remain unanswered, but several studies examining differential gene expression in keloid fibroblasts (KFs) have observed an upregulation of antiapoptotic genes such as p53, bcl-2, and PEA-15 [3,4]. But clinical and experimental data indicate that those factors are not able to explain all genetic development in keloid, and imply some other genes function in this process. Accumulating evidence had suggested that survivin could play important roles in cell growth, apoptotic resistance, and cell cycle control. Furthermore, it was confirmed that survivin inhibitors could suppress proliferation and induce apoptosis in a broad spectrum of tumor cells both in vitro and in vivo [5]. High levels of survivin correlate with abbreviated patient survival, unfavorable prognosis, resistance to therapy, and accelerated rates of tumor recurrence [6]. In this report, we propose that the same regulatory mechanism of apoptosis would exist in KF cells during the stage of keloid development.

Hypothesis

In past, many researchers focused on classic factors such as inflammation and growth factors in keloid pathophysiology, relatively neglected the importance of anti-apoptosis as a biological factor relating to keloid initiation and progression. Recent researches have shown survivin performs multiple functions in cancer formation and contributes significantly to apoptosis resistance and chemoresistance via pathways associated with cell survival, cell-cycle control, and regulation of mitosis [7–9]. According to our previous study, we hypothesized that apoptosis in keloid fibroblasts was most prominently suppressed, and they fail to undergo physiologically programmed cell death and continue to produce and secrete connective tissue beyond the period expected in normal scar formation, accounting for the progressive and hypertrophic nature of keloids. Survivin, as an important member of inhibitors of apoptosis proteins (IAP) family may play a vital role in keloid progression. The impact of survivin on apoptosis inhibition and proliferation promotion of KFs sheds light for the first

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time on keloid formation. Since survivin blockers have been applied in clinical trials for treatment of some kinds of tumors, our idea would provide with novel therapeutic implications for keloids that are associated with apoptosis.

Evaluation of hypothesis

Anti-apoptosis of keloids

Resistance of tumor cells to apoptosis is an important mechanism for tumor progression. Keloids are benign skin tumors with dermal proliferative disorders, which occur following trauma, inflammation, surgery, burns, and sometimes spontaneously. Increased cell proliferation, accounting for the progressive and hypertrophic nature of keloids, correlates with the failure of apoptosis, which may play a role in the process of pathological scarring.

The understanding of mechanisms by which keloids escape from apoptosis would be beneficial in the design and development of novel therapeutic strategies that warrant further investigations. A comparison of expression levels between healthy skin fibroblasts and keloid fibroblasts showed elevated levels of the proto-oncogenes bcl-2, c-jun and c-fos in keloid fibroblasts [10]. And mutations in p53 were also identified [11,12], which may increase cell proliferation and decrease cell death in dysregulated growth patterns. The two oncogenes ribosomal protein 18 and Stat-3, both important proteins for cell proliferation, may be linked to keloid pathogenesis [4,13]. Another important factor related to keloid formation may be a dysregulation of apoptosis [14,15]. There was evidence that keloid fibroblasts failed to undergo physiologically programmed cell death (apoptosis) and continued to produce connective tissue beyond the period expected in normal scar formation, which caused keloids formation [16]. It was noted that normal skin fibroblast cultures had a 2-fold higher percentage of apoptotic cells than keloid fibroblast cultures [17]. Keloids were more resistant to Fas-mediated apoptosis [18] and overexpression of insulin-like growth factor (IGF)-1 receptor inhibited ceramid-induced apoptosis [19]. Furthermore, expression of pro-apoptotic genes TRADD (TNF R-1 associated death domain) and cytoplasmic dynein light chain 1 (HDLC1) in human keloid tissue was significantly reduced versus those from normal scars [16]. Messadi et al. showed higher basal levels of TNF- receptor-associated factors (TRAF-1, TRAF-2, TNF-alpha), inhibitor of apoptosis (c-IAP-1), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) in keloids compared with normal skin [20].

On the other hand, the characteristics of tumor, such as rich vessels, high growth factors status and uncontrolled growth, were also the characteristics of keloids.

Survivin as an inhibitor of cell apoptosis

Survivin (BIRC5), as the smallest member of the family of inhibitors of apoptosis proteins (IAPs) [21], is now widely acknowledged as an orchestrator of cell division and inhibitor of apoptotic pathways. Overexpressed in virtually every human tumor, but undetectable or present at very low levels in most normal adult tissues, survivin expression has been consistently associated with disease progression, metastatic dissemination, resistance to therapy and death from disease.[7,21]. Suggested to be one of the most cancer-specific proteins identified to date, survivin acts as a signalling node in tumour maintenance and, after first promising results, is now attracting increasing attention as a target in anti-cancer therapy.

Survivin has been implicated in both control of cell survival and regulation of mitosis in cancer [21–23]. It was originally suggested that survivin counteract both intrinsic and extrinsic mediators of apoptosis, including IL-3 withdrawal, FAS stimulation, TRAIL, over expression of BAX, caspase −3, −7, and −8[21,24,25]. Compelling data accumulated over a decade have elucidated many of its essential roles as a regulator of mitosis, a broad cytoprotective factor, and an effector of cellular adaptation to stress. As "survivin networks" are dramatically exploited in cancer, survivin is known to regulate apoptosis, cytokinesis followed by interaction with heat shock protein (HSP90), second mitochondria-derived activator of caspases (Smac/Diablo), cyclin dependent kinase 4 (CDK4), cluster of differentiation 2 (CD2), retinoblastoma /E2F complex, and NF-kB [26]. Therefore, survivin is unanimously viewed as one of the most prominent cancer genes [8]. Survivin is up-regulated during cell division and is closely associated with centrosomes and mitotic spindle microtubules. It controls chromosome spindle-checkpoint assembly, thereby ensuring normal cell division. Survivin is maximally expressed during the G_2/M phase of the cell cycle and exists predominantly as a multi-protein complex, known as the chromosomal passenger complex (CPC) [27,28]. By functioning in this complex survivin can facilitate accurate sister chromatid segregation and stabilization of the microtubules in late mitosis [29]. Not only that, over-expression of survivin protein has been demonstrated to rescue cells from p53-induced apoptosis [30]. As the methods to inhibit fibroblast proliferation and induce cell apoptosis may be the effective path for keloids regression, the effect of survivin cannot be overlooked.

The action of survivin in angiogenesis

In addition to its direct role in carcinogenesis, survivin may also play a key role in tumor angiogenesis as it is strongly expressed in endothelial cells during the proliferative phase of angiogenesis [22,31,32]. Primary effectors of angiogenesis in tumors include VEGF (vascular endothelial cell growth factor) [33,34], bFGF (basic fibroblast growth factor) and PDGF (platelet-derived endothelial cell growth factor), which significantly lead to increased endothelial cell proliferation, migration, and survivial, they often coexpressed in the same tumor tissue, which exhibit remarkable synergistic activity on angiogenesis. [35,36–38]. VEGF, bFGF, PDGF, and angiopoietin-1 could enhance vascular endothelial cells proliferation by increasing survivin expression [39–41]. Furthermore, VEGF can stimulate survivin expression in neuroblastoma cells [42]. And Survivin has been shown to up-regulate the expression of VEGF and bFGF in glioma cells [43]. Therefore, there may be a positive feedback loop between survivin and angiogenesis factors to sustain tumor cells development and proliferation. Manipulating the survivin pathway may facilitate endothelial cell apoptosis and promote vascular regression during tumor angiogenesis [32].

Abnormal angiogenesis manifested by an imbalance between proangiogenic and antiangiogenic factors has been recognized as a "common denominator" underlying many pathological conditions including tumors and keloids. Studies on keloid angioarchitecture have revealed increased blood vessel density at the dermis juxtaposed to the lesion in contrast to an avascular collagenous nodule at the center [14]. Intriguing observations of abnormal biochemical, cellular, and physiological aberrations in keloids akin to a tumor have been reported. These include increased blood vessel density; hypoxia; upregulation of proangiogenic growth factors such as VEGF, connective tissue growth factor, and PDGF and so on [44–46]. VEGF levels both in keloid tissues and circulation were higher in keloid patients in comparison to normal controls [47–49]. Hence, antiangiogenic therapeutics in combination with current curative strategies as in tumors would present a scope for the effective management of keloids. With the role of survivin both in carcinogenesis and angiogenesis, its inhibition treatment would have dual effects in keloid.