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Review
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# Syndecan as a Messenger to Link Diabetes and Cancer

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## Abstract

Syndecans are membrane-anchored proteoglycans and implicated in the pathogenesis of cancer progression and metastasis. Syndecans also play important roles in interacting with growth factors, extracellular matrix and other cell surface molecules such as IGF-1 receptor. In the present review, we discuss about the syndecan structure, their role in signaling with other receptors, in addition to its general biology. The emerging roles of syndecans in the pathophysiology of human diseases, especially insulin resistance, diabetes and cancer is discussed.

**Key Words:** Syndecans, Insulin resistance, Diabetes and cancer

## INTRODUCTION

Cell surface syndecans are membrane-anchored proteoglycans. These glycoproteins have covalently linked glycosaminoglycan side chains. They interact via their extracellular part with various growth factors, extracellular matrix components, other cell surface molecules, and proteins involved in the regulation of blood coagulation. Thus the syndecans involve in synchronized expression patterns during embryogenesis and malignant transformation. These cell-cell interactions via their extracellular matrix ligands control cell proliferation, dynamic cytoskeletal remodeling, apoptosis and gene expression.

Over the last few years, it has been widely accepted that heparan sulfate proteoglycans play a role in growth control, cell spreading, cellular recognition, cellular adhesion, and signaling, possibly as co - receptors with integrins, IGF-1R and cell - cell adhesion molecules, including fibronectin, vitronectin, laminins, and the fibrillar collagens (Bernfield *et al.*, 1999; Woods, 2001; Alexopoulou *et al.*, 2007; Beauvais and Rapraeger, 2010). In addition, all syndecans have dibasic peptide sequence adjacent to the plasma membrane. Thus, the extracellular domains of syndecans could be cleaved by extracellular proteases. Syndecan's ectodomains have been shown to regulate a multitude of biological functions in cell-dependent and cell-independent approaches (Li *et al.*, 2002; Endo *et al.*, 2003; Elenius *et al.*, 2004). Soluble syndecans also convert the membrane-bound receptors into soluble effectors/or antagonists. The soluble ectodomains of syndecans can compete with intact syndecans for extracellular ligands (Steinfeld *et al.*, 1996). In this review, we will discuss the general features and their conventional roles in signaling with co-receptors. Finally, we will explore the emerging roles of syndecans in the pathophysiology of human diseases, especially type 2 diabetes.

## SYNDECAN STRUCTURE

All the syndecans are a type 1 transmembrane proteins that are expressed in almost every cell of the body. Four members of syndecan family have been identified in mammalians such as syndecan-1, 2, 3, and 4. Syndecan-1 analogs are also identified in other mammals such as mouse, rat, dog, chimpanzee, guinea pig, Chinese hamster, cat and chicken. The extracellular domains of human and mouse syndecan-1 display approximately 70% sequence homology whereas the transmembrane domain and cytoplasmic domain show 96 % and 100% sequence homology, respectively. Synthesis of four syndecan core proteins are mediated by 4 distinct cDNAs (Couchman, 2003).

The core protein contains 3 domains, an ectodomain (extracellular domain), transmembrane domain, and cytoplasmic domain. The ectodomain contains a cleavable amino terminal single peptide and the glycosaminoglycan attachment sites. There are 3 highly conserved serine-glycine sites for heparan sulfate attachment (amino acids 37,45 and 47) near the N terminal of the core protein and 2 highly conserved serine-glycine sites for chondroitin sulfate attachment (amino acids 210 and 220), adjacent to the cell membrane. Protease cleavage sites contain basic amino acids and they are located to

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the transmembrane portion of the protein core. The cleavage sites are related to shedding of the proteioglycan. The transmembrane domains are highly conserved among the syndecan family members from different species, since only a few amino acids differ among the vertebrate sequence. These domains contain a unique sequence of glycine/alanine that is involved in interactions with other membrane proteins and for their membrane localization.

The cytoplasmic carboxyl-terminal is contains 2 highly conserved regions with about 30 amino acids, which are same in all syndecan family members. However, syndecan-2 has a substitution of arginine for lysine. The C1 region at juxtamembrane region has been suggested to play an important role in binding protein FERM domains. The C1 region is well conserved among the syndecan family except a conservative R for K amino acid substitution in syndecan-3 (Cohen *et al.*, 1998; Granes *et al.*, 2000). The C2 region located at carboxyl terminal bearing the amino acid sequence of EFYA is present in all sydecan family members and has the ability to bind with type II PDZ domain which is important in protein-protein interactions. It binds specifically to the carboxyl termini of various transmembrane receptors, and rearranging cell membrane-associated proteins (Fanning and Anderson 1996; Songyang *et al.*, 1997). Interestingly, PDZ domain-containing proteins associate with many signaling proteisn, including syntenin, cortactin, and calcium/calmodulin dependent serine protein kinase (CASK) (Grootjans *et al.*, 1997; Gao *et al.*, 2000; Ethell *et al.*, 2000). A central variable region (V) is located between C1 and C2 that differs in each family member. The sequence of variable domain (V) for syndecan-1 is SLEEPKQANGGAYQKPTKQE. The cytoplasmic domain is important in interacting with cytoskeletal preteins. A tyrosine residue on the cytoplasmic domain is essential in the interaction. The V region plays critical role in bundling of actin as well as cell migration. Fig. 1 displays that a general feature of structures of syndecans.

Each syndecan family member has a unique pattern of expression in terms of time and space. Syndecan-1 is primarily expressed in epithelial and plasma cells; Syndecan-2 is mainly expressed in fibroblasts, endothelial cells, neurons, and smooth muscle cells; Syndecan-3 is the major syndecan in the nervous system, but it is also important for chondrocyte proliferation; and syndeca-4 is nearly ubiquitous. Recent study suggested that both sydenca-2 and syndecan-4 exert important role in osteoblast cell adhesion and surviaval (Wang *et al.*, 2011). Interestingly, syndecan-1 has been suggested to play a role I gingival inflammation (Kotsovillis *et al.*, 2010).

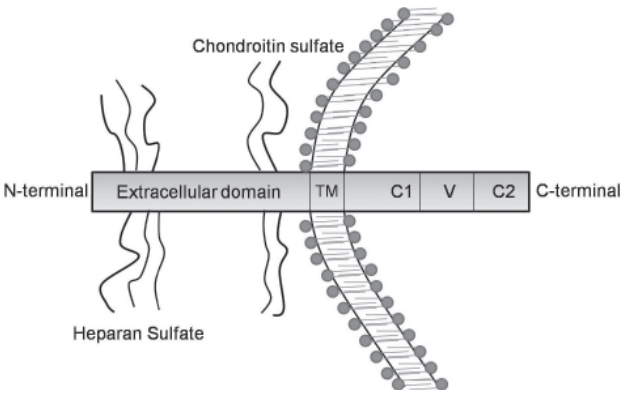


**Fig. 1.** Schematic stucure of syndecan functional domain. Syndecan can bear both heparan and chondrotin sulfate chains at 37, 45 and 47 and 210 and 220 of amino acid sequence respectively. Protease cleavage sites composed of basic amino acids are found close to the transmembrane (TM) portion of the protein core and are related to shedding of the proteioglycan from the cell surface. Ectodomains of the syndecan core proteins are highly divergent both in size and sequence. This indicates that the domain may confer separate and unique functions.

## INSULIN RESISTANCE AND CANCER

In past several years, there have been a number of interesting research publications showing that the association between the cancer risk and the different components of metabolic syndrome. However, the epidemiological studies linking metabolic syndrome to cancer are scarce. Adiposity induces adverse local and systemic effects that include adipocyte intracellular lipid accumulation, endoplasmic reticulum and mitochondrial stress, and insulin resistance, with associated changes in circulating adipokines, free fatty acids, and inflammatory mediators. In a study of insulin and fasting glucose and risk of recurrent colorectal adenomas, Flood et al, noted that patients with increased insulin and glucose are at higher risk of adenoma recurrence, and for those with increased glucose, the increase in risk for recurrence of advanced adenomas is even greater (Flood *et al.*, 2007).

Abundant data also showing that over expression of IGF-1 receptors on multiple human cancers, it is believed that the effects of insulin on cancer cell proliferation *in vivo* may involve an indirect mechanism, such as IGF-1 stimulation. Growth hormone is the primary stimulus for IGF-1 production in the liver and insulin can stimulate IGF-1 production by up-regulating growth hormone receptors in the liver. Hyperinsulinemia can also increase IGF-1 bioavailability by decreasing hepatic secretion of IGF-binding protein (IGFBP)-1 and -2 (Cowey and Hardy, 2006). IGF-1 has important proliferative and anti-apoptotic effects in tumorigenesis. Angiogenesis is also stimulated by IGF-1 because it increases vascular endothelial growth factor (VEGF) production, which has been shown in breast and colon cancer cell lines. Activation of the IGF-1 receptor also stimulates the p21 ras/MAPK pathway for cell proliferation and the $PI_3$K/Akt cell survival pathway (Hoeben *et al.*, 2004; Ibrahim and Yee, 2004). Hyperinsulinemia and IGF-1 are also believed to inhibit the synthesis of the sex hormone-binding globulin (SHBG), increasing levels of free sex hormones and promoting sex hormone-dependent cancers such as breast, endometrial, and prostate cancers (Calle and Kaaks, 2004). Also increasing evidence exists now that castration therapies used in prostate cancer may lead to hyperinsulinemia and raises concern for potential recurrence risk (Smith *et al.*, 2006). Thus, hyperinsulinemia has been linked to neoplastic proliferation of various organ cells.

## SOLUBLE SYNDECANS AND TUMOR

Expression of syndecans and the structure of their haparan sulfate is changed during development (Sun *et al.*, 1988) and in transformed epithelial (Inki and Jalkanen, 1996; Bayer-Garnet, 2001) are associated with an epithelial-mesenchymal

transformation with attendant alterations in cell morphology, motility, growth and differentiation.

These changes play important roles in tumor pathophysiology (Beauvais and Rapraeger, 2004; Sanderson, 2001; Fears and Woods, 2006). It has been suggested that syndecan-1 is involved in Wnt-1 induced tumor in the mouse mammary gland (Alexander *et al.*, 2000). It has been found that syndecan-1 promotes the metastases in lung squamous carcinoma cells (Hirabayashi *et al.*, 1998). The overexpression of syndecan-1 expression has been observed in various cancer such as pancreatic (Conejo *et al.*, 2000), gastric (Wiksten *et al.*, 2001) and breast (Stanley *et al.*, 1999; Barbareschi *et al.*, 2003; Burbach *et al.*, 2003) carcinomas.

Interestingly, a number of papers have been published to indicate syndecan-1 is an inhibitor of carcinogenesis. Decrease of syndecan-1 expression is associated with epithelial cancers and in pre-malignant lesions of the oral mucosa (Soukka *et al.*, 2000) and uterine cervix (Inki *et al.*, 1994a; Nakanishi *et al.*, 1999; Rintala *et al.*, 1999). Tumor progression is found when syndecan expression is normalized (Hirabayashi *et al.*, 1998; Sanderson, 2001; Numa *et al.*, 2002). Loss of syndecan-1 correlates with a reduced survival in squamous cell carcinoma of the head, neck and lung (Inki *et al.*, 1994b; Nackaerts *et al.*, 1997; Anttonen *et al.*, 1999), laryngeal cancer (Pulkkinen *et al.*, 1997; Klatka, 2002), multiple myeloma (Sanderson and Borset, 2002), malignant mesothelioma (Kumar-Singh *et al.*, 1998) and a high metastatic potential in hepatocellular and colorectal carcinomas (Levy *et al.*, 1996; Levy *et al.*, 1997; Matsumoto *et al.*, 1997; Fujiya *et al.*, 2001). These controversies in the dual roles of syndecan-1 in tumorigenesis could be due to tissue- and tumor stage-specific functions of the protein.

Heparan sulphate-mediated binding of extracellular ligands is critical to the function of the syndecan. Strikingly, ectopic expression of syndecan-1 in syndecan-deficient myeloma cells prevented invasion, while the expression of other cell surface heparan sulfate proteoglycans (e.g., glypican) had little such effect, raising the importance of the binding characteristics between extracellular ligands and heparan sulfate. It has been found that there are variations in binding affinity of extracellular ligands to syndecans and the ligand-syndecan bindings are not specific. These results support the hypothesis that the syndecan family may not work as a classical receptor.

It is reasonable to propose that the syndecan functions as a core protein and its shed form. It has been identified that syndecan-1 can be shed by heparanase from the cell surface (Yang *et al.*, 2007) via stimulation of ERK that leads to MMP-9, a syndecan-1 sheddase, expression (Purushothaman *et al.*, 2008). A more recent study indicated that heparanase also regulates levels of syndecan-1 in the nucleus (Chen and Sanderson, 2009). A number of potential roles of heparan sulfate in the nucleus have been suggested for regulation of cell proliferation, inhibition of DNA topoisomerase I, inhibition of histone acetyltransferase (HAT), control of cell division, and nuclear localization of basic FGF (Fedarko *et al.*, 1989; Kovalszky *et al.*, 1998; Brockstedt *et al.*, 2002; Dobra *et al.*, 2003; Hsia *et al.*, 2003). The shed syndecans via their heparin sulfate chains are active and working as a signaling mediators for cell-cell interaction, cell survival, cell migration (Couchman *et al.*, 2001; Perrimon and Bernfield, 2001; Sanderson, 2001; Couchman, 2003; Beauvais and Rapraeger, 2004; Tkachenko *et al.*, 2005). Interestingly, it has been found that insulin promotes shedding of syndecan ectodomain, suggesting a potential link between insulin signaling and syndecan-mediated celluar events such as cancer progression (Reizes *et al.*, 2006).

## INSULIN LIKE GROWTH FACTOR AND CANCER

Abundant data showing that overexpression of IGF-1 receptors has been implicated in the pathogenesis of many cancers. Recently, it has been found that syndecan-1 interacts with IGF-1 receptor to activate integrin (Beauvais and Rapraeger, 2010). It is reasonable to speculate insulin on cancer cell proliferation *in vivo* may involve an indirect mechanism, such as IGF-1 stimulation. Growth hormone is the primary stimulus for IGF-1 production in the liver and insulin can stimulate IGF-1 production by up-regulating growth hormone receptors in the liver. Hyperinsulinemia can also increase IGF-1 bioavailability by decreasing hepatic secretion of IGF-binding protein (IGFBP)-1 and -2 (Cowey and Hardy, 2006). IGF-1 has important proliferative and antiapoptotic effects in tumorigenesis. Angiogenesis is also stimulated by IGF-1 because it increases vascular endothelial growth factor (VEGF) production, which has been shown in breast and colon cancer cell lines. Activation of the IGF-1 receptor also stimulates the p21 ras/MAPK pathway for cell proliferation and the PI3K/Akt cell survival pathway (Hoeben *et al.*, 2004; Ibrahim and Yee, 2004). Hyperinsulinemia and IGF-1 are also believed to inhibit the synthesis of the sex hormone-binding globulin (SHBG), increasing levels of free sex hormones and promoting sex hormone-dependent cancers such as breast, endometrial, and prostate cancers (Calle and Kaaks, 2004). Also increasing evidence exists now that castration therapies used in prostate cancer may lead to hyperinsulinemia and raises concern for potential recurrence risk (Smith *et al.*, 2006). Thus, hyperinsulinemia has been linked to neoplastic proliferation of various organ cells.

Various epidemiological studies are indicating a link to insulin resistance or hyperinsulinemia with various epithelial cancers. Initial studies done in prostate cancer showed a correlation with plasma IGF-1 levels (Chan *et al.*, 1998). Subsequently, various studies have confirmed high levels of IGF-1 and insulin levels associated with prostate cancer risk prospectively (Harman *et al.*, 2000; Kaaks *et al.*, 2003; Giovannucci *et al.*, 2004). A link between breast cancer risk and hyperinsulinemia (measured by fasting C-peptide levels) has been shown mainly in postmenopausal breast cancer (Verheus *et al.*, 2006). High insulin levels have also been shown to be associated with risk of endometrial cancer independent of estradiol (Gunter *et al.*, 2008).

## DIABETES AND CANCER

It has been suggested that men with type 2 diabetes are less likely than nondiabetic men to develop prostate cancer. Recent genetic studies have highlighted a potential genetic link between the two diseases. Two studies have identified a version (allele) of a variant in the HNF1B (also known as TCF2) gene that predisposes people to type 2 diabetes, and one of them showed that the same allele protects men from prostate cancer (Frayling *et al.*, 2008). Colorectal carcinoma and type 2 diabetes mellitus share common risk factors and

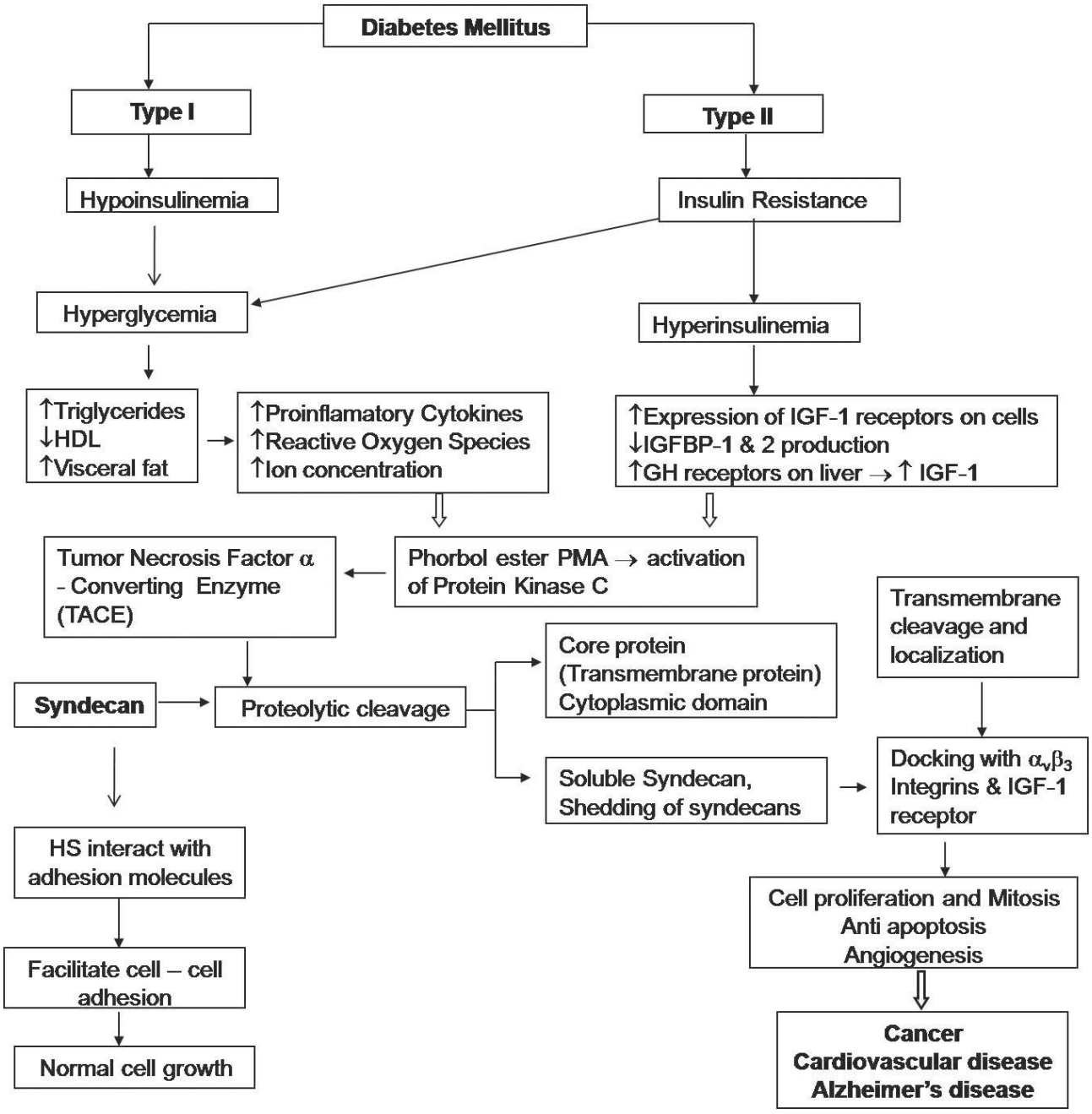


**Fig. 2.** Potential syndecan-mediated signal transduction bridging diabetes and cancer. Hypothetical signaling pathways of syndecans are proposed. Both type 1 and type 2 diabetes could lead to proteolytic cleavage of syndecans. These eventually could play a role in cancer pathology.

type 2 diabetes mellitus is associated with an increased risk of colorectal cancer. The increased risk occurs in both sexes (Yang *et al.*, 2005; Berster and Goke, 2008). The hyperinsulinemia hypothesis is based on the premise that elevated plasma levels of insulin and free IGF-1 promote the proliferation of colon cells and confer a survival benefit upon transformed colon carcinoma cells. Chronic insulin therapy was associated with increased colorectal adenoma risk among type 2 diabetes mellitus patients (Yang *et al.*, 2004; Chung *et al.*, 2008). It has also been reported that Type 1 diabetes is associated cancer risk in a population-based study (Zendehdel *et al.*, 2003). It is well accepted that inflammation is closely associated with diabetes: TNF-α converting enzyme (TACE) activity as well as TNF-α is increased in diabetic patients (Fornoni *et al.*, 2008; Monroy *et al.*, 2009). Considering the fact that shedding of syndecan-1 is paralled by TNF-α release, it is possible that diabetes could be lead to cancer development via TACE and TNF-α system (Andrian *et al.*, 2005).

## PROSPECTIVES

A significant body of evidence supports the possibility of connection between diabetes and cancer: a hypothetical model of syndecan signaling is proposed in Fig. 2. It will be necessary to clarify the potential role of syndecans in the progression of cancer with diabetes. Interactions between syndecans and insulin receptor, IGF-1 receptor, IRS-1 and integrin may be important players for syndecans to induce cancer via diabetes. These research will eventually provide promise for the rational design of new drugs that will prevent and/or treat cancer as well as metabolic syndromes induced by insulin resistance such as osteoporosis, periodontal diseases and diabetes mediated bone destruction.

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