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TOPICAL REVIEW

Regulation of Renal Cell Carcinoma Cell Proliferation, Invasion and Metastasis by Connexin 32 Gene

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Abstract Gap junctions composed of connexin (Cx), a large protein family with a number of subtypes, are a main apparatus to maintain cellular homeostasis in many organs. Gap junctional intercellular communication (GJIC) is actively involved in all aspects of the cellular life cycle, ranging from cell growth to cell death. It is also known that the Cx gene acts as a tumor-suppressor due to the maintenance of cellular homeostasis via GJIC. In addition to this function, recent data show that the GJIC-independent function of Cx gene contributes to the tumor-suppressive effect of the gene with specificity to certain cells. With respect to the tumor-suppressive effects, Cx genes acts as tumor-suppressors in primary cancers, but the effects are still conflicting in invasive and metastatic cancers. We have previously reported that Cx32 is specifically down-regulated in human renal cell carcinoma (RCC) cell lines as well as cancerous regions when compared to normal regions in kidneys. In recent studies, we have also reported that Cx32 suppresses growth, invasion and metastasis of RCC cells. In this minireview, we refer to a new aspect of Cx32-dependent functions against cell proliferation, invasion and metastasis in RCC cells, especially in a GJIC-independent manner.

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Introduction

Among the different types of cell-cell interaction in mammalian cells, gap junctional intercellular communication (GJIC) is considered to be the only route allowing direct transfer of ions and hydrophilic molecules of up to 1,000–1,500 daltons in size between cells, thereby maintaining the electrical and metabolic cell homeostasis (Mesnil & Yamasaki, 1993; Saez et al., 1989; Simpson, Rose & Lowenstein, 1977). The gap junction is made up of juxtaposed transmembrane hemichannels (connexons) provided by adjacent cells, and each connexon consists of six individual transmembrane proteins called connexin (Cx) (Stauffer et al., 1991; Paul, 1995). In general, it is well established that the Cx gene acts as a tumor-suppressor gene by maintaining homeostatic control in multicellular organisms. Currently, at least 20 different Cx genes have been cloned in humans (Willecke et al., 2002). Different combinations of Cx genes are expressed in different tissues with temporal specificity during development or tissue differentiation (Paul, 1995). Such rigid regulation of Cx expression may contribute to cell differentiation and cell growth in multicellular organisms by keeping important signals, such as those involved in growth control, at equilibrium among GJIC-connected cells.

Vast lines of evidence strongly support the hypothesis that Cx genes act as tumor-suppressors (Fitzgerald & Yamasaki, 1990). Tumor-promoting agents and oncogenes disrupt Cx-mediated GJIC, whereas antitumor agents such

as retinoids upregulate GJIC (Trosko, Madhukar & Chang, 1993). Decreased or diminished expression and function of Cx genes is usually observed in most tumor cells (Yamasaki & Naus, 1996). Furthermore, cells derived from Cx43 gene knockout mice had a higher tendency for tumorigenesis compared with wild type (Martyn et al., 1997). More direct evidence for the tumor-suppressive effect of Cx genes has been obtained by transfection of the genes into noncommunicating tumor cells (Rae et al., 1998). In transfected tumor cells, Cx genes conferred a reduced growth rate in culture as well as in nude mice. Recent reports, including our study, have suggested that not all Cx genes are able to exert a tumor-suppressive effect on a given tumor but, rather, that there seems to be a Cx-cell type compatibility for this effect (Bond et al., 1994; Yano et al., 2001). That is, Cx exerts growth control only in tissues or cell types in which the particular Cx is naturally expressed. At present, the tumor-suppressive effect of this gene has been clearly established in primary cancers, but the role of Cx genes in progressive and metastatic cancers is unclear and, at best, seems to be very limited (Holder, Elmore & Barrett, 1993; Nicolson, Dulski & Trosko, 1988). In one study, we reported that Cx26 was expressed and acted as a tumor-suppressor gene in liver cancer (Yano et al., 2001). We also found in the same study that Cx26 expressed in the progenitor cell of liver cancer inhibits cellular invasiveness which is involved in the process of cancer metastasis. From this report, it can be postulated that the Cx gene, when it is expressed in the progenitor cell and has a tumor-suppressive effect against primary cancer, also acts as a tumor-suppressor in progressive and metastatic cancers.

In our previous study, we showed that Cx32 is expressed in the progenitor cell of renal cell carcinoma (RCC), is downregulated in cancerous regions of human kidneys and acts as a tumor-suppressor gene in metastatic as well as primary RCC (Yano et al., 2003; Fujimoto et al., 2004, 2005). Also, we suggested some possible mechanisms for the tumor-suppressive effects of Cx32 in primary and metastatic RCC in these reports. Here, we discuss the regulation of cell proliferation, invasion and metastasis in RCC cells by Cx32.

Downregulation of the Cx32 Gene in RCC

As mentioned, Cx genes are frequently downregulated during carcinogenesis, and the Cx gene preferentially exerts a tumor-suppressive effect on the tumor from normal progenitor cells in which the particular Cx gene is naturally expressed (Mesnil, 2002). Thus, to examine the Cx gene as a tumor-suppressor gene in each tissue, it is required to determine the Cx subtype specifically expressed in the progenitor cell of each tumor. In this context, we determined the Cx gene that is downregulated during the carcinogenic process in human kidneys. In a previous study, we showed that of the Cx subtypes, Cx32 is specifically downregulated in RCC from maintenance hemodialysis patients compared to noncancerous regions of the kidney from the same patients (Yano et al., 2003). Also, microarray analysis has demonstrated that the expression level of Cx32 mRNA in several types of RCC is lower than that in normal kidneys. Furthermore, we have confirmed that Cx32 is downregulated in several RCC cell lines and that Cx32 is expressed in human renal proximal tubular cells (a progenitor cell of RCC) (Yano et al., 2003; Hirai et al., 2003). These results suggest that Cx32 acts as a tumor-suppressor gene in RCC.

Cell Growth Control in Primary and Metastatic RCC Cells by Cx32

We have reported that Cx32 acts as a tumor-suppressor gene in metastatic RCC (Caki-1) as well as primary RCC (Caki-2) cells (Fujimoto et al., 2004, 2005). In primary RCC cells, Cx32 reduced several malignant phenotypes related to tumor cells. Of the malignant phenotypes, Cx32 especially restored contact inhibition of the RCC cells; i.e., Cx suppressed the cell growth rate at high cell density. In order to determine which signal molecule mainly contributes to the restoration of contact inhibition, we compared the activation status of several growth factors in RCC cells before and after Cx32 expression. We found that Cx32 induces the restoration of contact inhibition via the inactivation of Her-2 in a GJIC-independent manner. It has been reported that the Her-2 activation induces multilayering of epithelial monolayers through destruction of tight junctions, leading to disruption of cell polarity and loss of contact inhibition (Muthuswamy et al., 2000). Additionally, Cx32 can restore tight junctions through interaction with occludin and ZO-1 in hepatocytes (Kojima et al., 1999, 2002). We also observed that Cx32 could reinduce occludin in RCC cells. Taken together, we conclude that Cx32 restores the contact inhibition of RCC cells through the maintenance of cell polarity, due to suppression of Her-2 activation.

In metastatic RCC cells, Cx32 expression drastically suppressed the development of RCC cells in nude mice, and the suppressive effect was mainly due to inhibition of cell-driven vascular endothelial growth factor (VEGF) production (Fujimoto et al., 2005). All tumors must undergo angiogenesis or neovascularization to acquire nutrients for continued growth and metastatic spread (Folkman, 1995), and VEGF is the most important inducer of angiogenesis (Folkman, 1995; Grunstein et al., 1999). Thus, we

speculated that a main target molecule of Cx32 would be one that stimulates VEGF production. The overexpression/activation of Src has been reported in several types of cancers, including RCC, and the kinase is believed to play a critical role in tumor growth, angiogenesis, invasion and dissemination (Laird et al., 2003; Irby & Yeatman, 2000; Yonezawa et al., 2005). Based on these reports, we hypothesized that Cx32-dependent suppression of Src activation could contribute to the inhibition of VEGF production from RCC cells *in vivo*. Actually, we confirmed that Cx32 suppressed VEGF production via inactivation of Src in RCC cells and that the effect occurred in a GJIC-independent manner (Fujimoto et al., 2005). This inactivation of Src leads to wide-ranging inhibition of several signal molecules located downstream in the Src signal pathways, such as Her-2 (Ren & Schaefer, 2002). Of the downstream molecules of Src signaling, we determined that the signal transducer and activator of transcription 3 (Stat3) is a key transcription factor inducing VEGF in RCC (Fujimoto et al., 2005). These results suggest that Cx32 suppresses VEGF-triggered angiogenesis via inactivation of Src-Stat3 signaling in metastatic RCC cells.

Regulation of Invasion and Metastasis in Metastatic RCC Cells by Cx32

In order to examine if Cx32 could reduce the metastatic potential of metastatic RCC cells, we established a novel metastasis model of human RCC in SCID mice depleted of natural killer (NK) cells. Since NK cells are known to play a critical role in the eradication of circulating tumor cells and depletion of the cells leads to enhancement of metastasis of solid tumor cells, we deleted NK cells in SCID mice, using anti-interleukin-2 (IL-2) receptor β–chain antibody (TM-β1), which has potential to reduce NK cells *in vivo* (Byrne, Bouchier-Hayes & Harmey, 2005; McMahon et al., 2001). In this model, we have demonstrated that Cx32 expression in metastatic RCC cells almost abolished the metastatic potential of RCC cells in lung and liver (Yano et al., 2006). Linked to this finding, serum levels of type-1 plasminogen activator inhibitor (PAI-1) and VEGF, which were important factors in the process of invasion and metastasis of cancer cells, were reduced by Cx32. Also, we have confirmed that Cx32 reduces *in vitro* the invasion capacity of RCC cells due to downregulation of fibrinolytic factors including PAI-1 via the inactivation of Src signaling (Hagiwara et al., 2006). These results suggest that Cx32 acts as a potential anti-invasive and antimetastatic gene against metastatic RCC. In general, tumor cells undergo adaptive changes that allow them to survive and proliferate in hypoxic environments, leading to aggressive tumor behavior, and hypoxic tumor cells are resistant to most anticancer agents (Semenza, 1998). A key event of hypoxia adaptation in tumor cells is to induce hypoxia-inducible factor (HIF) via the activation of Src because HIF acts as a potential inducer of genes required for invasion and metastasis under hypoxia including PAI-1 and VEGF (Jiang et al., 1997; Li et al., 2005). As mentioned, we have reported that Cx32 reduced production of PAI-1 and VEGF in metastatic RCC cells via inhibition of Src signaling. Taken together, it appears that inhibition of hypoxic adaptation of metastatic RCC cells by Cx32 is key to reducing the invasive metastatic potential in RCC cells.

In our recent microarray analysis, we determined a promising candidate, other than Src, required for the Cx32-dependent suppression of hypoxic adaptation of metastatic RCC cells (Yano, 2007). In this analysis, we found that Cx32 upregulates fumarate hydratase (FH), which plays an essential role in the mitochondrial tricarboxylic acid cycle by catalyzing the conversion of fumarate to malate in metastatic RCC cells. In a recent report, loss of FH was directly associated with the development of renal cancer (Isaacs et al., 2005). When FH inhibition occurs in tumor tissues, the substrate of FH, fumarate, accumulates in mitochondria and subsequently leaks out to the cytosol, where it inhibits a family of prolyl hydroxylase enzymes (Selak et al., 2005). Since prolyl hydroxylase enzymes are required for degradation of HIF (Dann & Bruick, 2005), the FH inhibition in RCC can induce stabilization of HIF. Thus, it seems that the activation of FH by Cx32 plays a role in the Cx32-dependent suppression of hypoxic adaptation of metastatic RCC cells via the stabilization of HIF.

Cx32-Dependent Induction of Differentiation in Metastatic RCC Cells

It has been well established that Cx genes induce and maintain differentiation of each cell due to Cx-driven GJIC (Trosko & Ruch, 2002). In fact, the upregulation of GJIC might reduce several malignant phenotypes that occur in poorly differentiated neoplastic cells (Au et al., 2001). In our studies, we have also found that Cx32 induces redifferentiation in metastatic RCC cells (Fujimoto et al., 2005; Sato et al., 2007). In a previous study, cadherin-6 was required for cell-cell adhesion in normal proximal renal tubular epithelial cells (progenitor cells of RCC), and the downregulation of cadherin was closely related to RCC with histology associated with poor prognosis (Paul et al., 1997). This report suggests that the expression of cadherin-6 is a differentiated marker in proximal renal tubular epithelial cells. In our study, Cx32 restored the expression of cadherin-6 and cell adhesion potential in metastatic RCC cells (Fujimoto et al., 2005), indicating that Cx32 partly

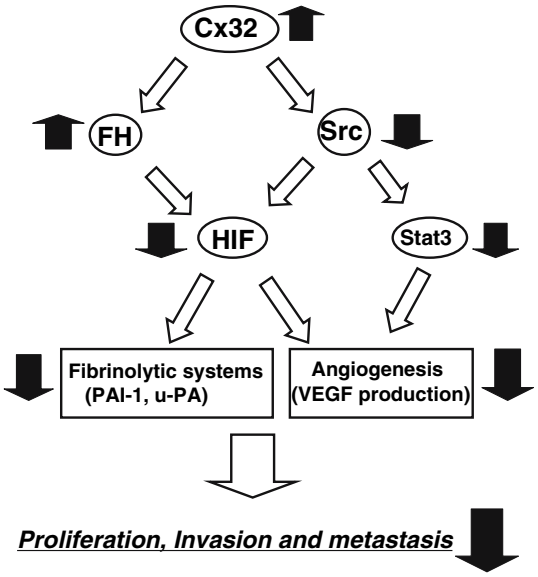

Fig. 1 Inhibitory effects of Cx32 on proliferation, invasion and metastasis in metastatic RCC cells

induces differentiation in metastatic RCC cells. In addition, we have observed that Cx32-transfected metastatic RCC cells were more sensitive to vinblastine (VBL) and that this was associated with decreased expression of P-glycoprotein (P-gp), the multidrug resistance-1 gene product (Ambudkar et al., 1999; Sato et al., 2007). Since overexpression of P-gp has been found in nearly 80% of RCC, chemoresistance of RCC to chemotherapeutic agents such as VBL in large part has been ascribed to P-gp (Naito et al., 1993). Severe chemoresistance of RCC is a representative malignant phenotype to show dedifferentiation in RCC, so Cx32-dependent reduction of P-gp expression indicates differentiation in RCC. With respect to a mechanism for the downregulation of P-gp by Cx32, we can speculate that the suppression of HIF by Cx32 leads to reduction of P-gp levels in RCC, based on a recent report that expression of P-gp in tumors is under the control of HIF (Wartenberg et al., 2003).

Conclusion

From our recent studies, we conclude that the Cx32 gene regulates cell proliferation, invasion and metastasis of metastatic RCC cells, mainly due to inhibition of hypoxic adaptation (Fig. 1). Cx32 suppresses the induction of HIF under hypoxia via the inactivation of Src and the upregulation of FH. The inhibition of HIF causes the inactivation of fibrinolytic systems and the inhibition of VEGF production, leading to regulation of RCC cell proliferation, invasion and metastasis.

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