Cancer as the most frequent cause of death worldwide requires detailed investigation of its biology. This knowledge may open a new possibilities of generating novel targets, help to overcome issues of drug resistance, improve therapeutic efficacy, and make disease treatment more successful. The major advance in recent years was the discovery of the cancer stem cells (CSCs) population responsible for tumor maintenance. Numerous signalling pathways and genes connected with stem cell biology, such as an alternation in multiple malignancies resulting from the WNT/β-catenin signalling pathway, have been identified. Crucial is knowledge concerning CSCs dependence and interactions with adjacent stromal cells that comprise a specialized microenvironment or niche. The niche shelters cells from diverse genotoxic factors thereby strengthening antitumor therapy resistance, and supports the growth of primary tumors converting non-tumorigenic cells into CSCs by processes related to the epithelial-to-mesenchymal transition (EMT). Moreover, numerous experiments confirmed that target genes of WNT signalling are implicated in cell-adhesion, which in consequence has an impact on EMT. This suggests a model that integrates a number of fundamental processes that underlie disease development and it should be put forward as an important target for novel therapies. Hence, linking the potency of silanol moiety, as innovative inhibitors of EMT resistant with the anticancerogenic properties of selenium agents that targeting genetic basis of cancer stem cells development, requires a need for a design, synthesis and evaluation of novel compounds as a prospective direction of cancer research.

**Key words:** cancer, cancer stem cells, cancer stem cell niche, epithelial-to-mesenchymal transition, matrix metalloprotease inhibitors, WNT/β-catenin signalling pathway, selenium, silicon
of normal cells (8). The β-catenin molecule is oncogenic protein which plays a crucial role in WNT signal transduction. The level of cytoplasm β-catenin is controlled by the activity of a destruction complex that is composed of the axin, the glycogen synthetase kinase 3β (GSK3β), and the adenomatosis polyposis coli protein (APC). In the absence of WNT signalling, GSK3β phosphorylates and consequently promotes degradation of cytoplasm β-catenin (Fig. 2). In turn, in the presence of WNT signalling, β-catenin undergoes accumulation in the cytoplasm and hence enters the nucleus. The nuclear β-catenin interacts with T cell (TCF) and lymphoid-enhancing transcription factors (LEF), inducing target genes expression that regulates cell cycle progression, apoptosis, and proliferation (9). Accordingly to these effects, it has been shown that inappropriate regulation and activation of WNT/β-catenin pathway can be associated with many disorders including cancer (10-12).

Thus, further investigation of the genetic basis of cancer development with particular focus on altered WNT signalling, seems to be strongly required as a significant step in improving of therapy targeting cancer stem cells.

SELENIUM-CONTAINING COMPOUNDS

Over the past decades large amount of evidences have been collected indicating that selenium compounds can be very good candidates for cancer treatment and chemoprevention. The inhibitory effect on cell growth with a preference only for tumor cells suggests their importance in modification and inhibition of carcinogenesis. Studies of the gene expression profile in tumor cells demonstrated that selenium-induced growth inhibition can be associated with modulation of the cell cycle, apoptosis and signalling (13-15). However, despite some promising investigations, still too little data is available to understand the exact mechanism and the molecular genetic determinants underlying the antitumor effects of selenium compounds. In addition, understanding of selenium mechanism of action is complicated due to multiplicity of chemical forms that may activate different molecular mechanisms with various toxicity and anticarcinogenic potential.

Selenium is a nonmetallic trace element recognized as an essential for human health which supplementation has been shown for many years to work as an anti-carcinogenic both in epidemiology and in in vitro studies (15). It has been demonstrated that anti-tumor activity of selenium can be associated with various mechanisms, like anti-oxidation (16), anti-inflammation (17), suppression of β-catenin by 1,4-phenylene bis (methylene) selenocyanate (p-XSC) (18, 19), and/or increased phosphorylation of mitogen-activated protein kinase (MAPK) by methylseleninic acid (MSeA) (20, 21). It has been reported that MSeA treatment of cancer cells may also inhibit β-catenin accumulation in the nucleus by increase in protein degradation (22). Another example might be significantly inhibited intestinal tumor formation caused by sodium selenite. This is associated with phosphorylation of JNK1 and subsequent inhibition of β-catenin and its transcriptional targets, what in consequence results in apoptosis induction and cell proliferation inhibition (23). Moreover, it has been shown that methylselenol, generated with seleno-L-
methionine, increases the expression of both prometastatic genes of matrix metalloproteases (pro-MMP-2 and pro-MMP-9), and antimetastatic genes of tissue inhibitor metalloproteases (TIMP-1 and TIMP-2). The final effect of these changes was shifted to the decrease of pro-MMP-2 activation with lowering migration and invasion potential of tumor cells (24).

Hence, ongoing research on selenium compounds should concentrate on above findings and provide detailed insights into the possible mechanisms of its anticancer properties, thereby leading to effective strategies to prevent cancer progression.

CANCER STEM CELL NICHE

Beside identification and description of CSCs biology, the knowledge concerning their dependence and interactions with adjacent stromal cells that comprise a specialized microenvironment or niche seems to be essential but seems to be little recognized so far (25). Each niche has a complex architecture and is composed of various stromal cells, soluble factors, blood vessels and extracellular matrix components. In physiological condition, stem cells reside in niches and the interaction with cells that comprise environment maintain them in quiescent state. Analogously, ongoing research suggests that CSCs depend on a similar environment, the CSC niche. This retain their ability to self-renew and give rise to more differentiated progenitor cells (25). Moreover, it was observed that the CSC niche has a protective role and by sheltering cells from diverse genotoxic factors can contribute to strengthened resistance of antitumor therapy (26, 27).

EPITHELIAL TO MESENCHYMAL TRANSITION

In addition to maintaining the CSC pool and supporting the growth of primary tumors, the niche plays a role in converting non-tumorigenic cells into CSCs by processes related to the epithelial-to-mesenchymal transition (EMT), also leading to tumor invasion and dissemination (28). Normally, the EMT plays important role in embryonic development with the formation of the body plan and differentiation of tissues and organs. The epithelial cell layer provide communication through gap junctions, and it is separated from adjacent tissues by a basal lamina. Inversely, mesenchymal cells are loosely organized and comprise connective tissues adjacent to epithelia. In consequence, the EMT involves phenotypic changes that include (a) the loss of cell polarity, (b) loss of cell-cell adhesion, and (c) the acquisition of migratory and invasive properties with resistance to apoptosis (29). Considering this facts in terms of tumorigenesis it can be crucial to know how this process is controlled and regulated.

Numerous experiments indicate that target genes of WNT signalling are implicated in cadherin mediated cell-adhesion, which in consequence may result in EMT. The most remarkable of these target genes encode the transcription factors Twist and Slug which directly inhibit the E-cadherin gene promoter. Other WNT/β-catenin target genes encode matrix metalloproteases (MMPs) or the cell-adhesion molecule L1 which provide to the E-cadherin degradation (30-34). These factors provide a mechanism whereby cadherin loss and increased WNT signalling induce EMT in normal development but also in carcinomas where disruption of intercellular contacts can result in dedifferentiation and invasiveness of human carcinoma cells.

Among variety of signals received by cells from the tumor microenvironment that have influence on WNT signalling, hypoxia is one of those worth mentioning. Experimental procedures, revealed that EMT-related events can be induced by hypoxia and occur through a biphasic mechanism involving (a) early and reactive oxygen species (ROS)-dependent inhibition of GSK-3β, followed by early SNAIL nuclear translocation and E-cadherin down-regulation, and (b) a later migration and invasiveness, also involving nuclear translocation of β-catenin, sustained by late and hypoxia-inducible factor (HIF-1α)-dependent release of vascular endothelial growth factor.
Interestingly, observations indicating redox mechanisms as significant in hypoxia-dependent EMT programme seems to be of crucial importance especially in the light of increasing interest in cellular redox modulation by selenium compounds. Certain selenium compounds like sodium selenite, methylseleninic acid, and methylselenol have been shown to alter cellular redox homeostasis in tumor cells and/or disrupt mitochondrial function that may be essential for their anticancer properties (38) (Fig. 3). Selenium is considered as an essential trace element and has been shown to afford an antioxidant protection and the redox-regulation in humans. Selenium is not only an essential constituent of extracellular and cellular metalloenzymes but also an important constituent of glutathione peroxidase (GPx), thioredoxin reductase and other selenoproteins. It is known that an increased generation of reactive oxygen metabolites can lead to DNA damage and mutation, resulting cellular carcinogenesis. Previous studies revealed that several adverse effects of radiotherapy and chemotherapy in cancer patients have been linked to oxidative cell processes in the human body (39). Interestingly, selenium supplementation may protect healthy tissues and reduce the side effects of radiotherapeutic and chemotherapeutic treatments (39, 40). Selenium triggers antioxidizing enzymes GPx, SOD and CAT activities and enhances the total cell antioxidant activity. This leads to enhancement of radical scavenging activity, the reduction of DNA damage and protection against the attack of reactive oxygen metabolites and radical cell damage. Besides the antioxidant activity, selenium compounds were shown to inhibit the growth of various cancer cells in vitro and to arrest cells at G1-S and G2/M transitions in a p53-dependent manner suggesting that selenium could mediate tumor cell arrest and apoptosis during therapy of various cancers (40-44). This inhibition of growth via an activation of p53 may depend upon an stimulation of many genes involved in post transcriptional activation, cell death due to apoptosis and DNA repair process (39, 43, 44) (Fig. 3).

MATRIX METALLOPROTEASE INHIBITORS

Mentioned above matrix metalloproteases (MMPs) mediate homeostasis of the extracellular matrix. Because of their multiple signalling activities that can be altered during carcinogenesis they might serve as the target for antitumor drugs. The key challenge yet to be done to use MMP inhibitors as a tool to combat MMP-mediated EMT, and in consequence cancer progression, seems to be (a) identification of the individual MMP targets implicated in EMT-triggered malignancy at specific points in cancer growth, and (b) development of therapeutic molecules targeting these MMPs with high selectivity (45-47). Thus, bringing a matrix metalloproteinase inhibitor to the point of clinical value seem to provide an additive effect to cytotoxic agents in multidimensional treatment regimens for many types of cancer.

SILICON-CONTAINING COMPOUNDS

The mechanism of the beneficial anti-cancer effect of selenium could be attributed its antioxidizing activity due to reduction of oxidative stress, the stabilization of the DNA and promotion of its repair after DNA damage as well as the inhibition of tumor-associated increase in angiogenesis and detoxification of pro-carcinogenic agents (Fig. 4). Similar as for selenium derivatives and the idea of their application as anti-cancer compounds, the most challenging aspect in optimization of MMP inhibitors in anti-cancer therapy is to search for candidates characterized by the acceptable pharmacological, pharmacokinetic and selectivity profiles and safe to the host cells. Cancer clinical trials giving not promising results have led to discussion on possibilities to obtain adequate MMP selectivity in order to minimize side effects (48). Searching for novel and optimized therapies focused on analogs or derivatives of existing drugs modified in their chemical structure, seems to be the mile stone in the coming years.
Silicon as the second most abundant chemical element and the one most similar to carbon seems to represent an important option in the quest for discovery and improvement of bioactive compounds absent in natural world (49). Significant differences caused by replacement of carbon by silicon atoms can be noticed in changed electro negativity, bond length and bond angles which results with different way of interaction with specific proteins and finally different pharmacology and pharmacodynamic properties. Moreover, comparing to carbon, silicon-containing compounds are generally more lipophilic. This property is very important especially in distribution of drug where increased lipophilic properties results in increased tissue penetration due to lipid-soluble properties of cell membrane (50).

Over the past decade the organosilane compounds has been introduced as a new isosteres, that represent good mimics of the tetrahedral intermediate formed during peptide bond hydrolysis, mainly because of their reluctance to dehydrate as opposed to the carbon equivalents. Thus, replacement of a carbonyl group with silanol or silanediol would create a transition state analogue with application as novel matrix metalloprotease (MMP) inhibitors that can become a very attractive approach in modern drug design (51).

CONCLUDING REMARKS

Since the WNT pathway and the regulation of cell-adhesion are strongly linked with a number of complementary mechanisms, this suggests a model that integrates a number of fundamental processes that underlie disease development. Understanding of this model seem to be of crucial importance for primary tumor growth as well as metastasis formation and it should be put forward as an important target for novel therapies. Selenium compounds and other chemopreventive agents that target the epigenome such as folate, retinoic acid and dietary sources including polyphenols from green tea, apples, coffee, lycopene and sulphoraphane were proposed as relevant in the mechanisms of health promotion and cancer prevention. However, so far, the evidence on their efficacy is derived mainly from in vitro investigations and these results should be confirmed in relevant animal models and human intervention studies. Thus, linking the potency of silanols moiety, as protease inhibitors, with the anticancerogenic activity of selenium agents that targeting genetic basis of cancer stem cells development, like altered in multiple malignancies WNT/β-catenin signalling pathway, gives a design, synthesis and evaluation of novel compounds as an extremely prospective direction of cancer research and hold great promise to improve treatment’s efficacy and outcome.

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Author’s address: Dr. Edyta Korbut, Department of Physiology Jagiellonian University Medical College, 16 Grzegorzecka Street, 31-531 Cracow, Poland.

E-mail: edyta.korbut@uj.edu.pl