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The Central Role of Survivin in Proliferation and Apoptosis of Malignant Pleural Mesothelioma

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1. Introduction

Malignant pleural mesothelioma is the most common mesothelial malignancy, which arises from the malignant transformation of mesothelial cells that line the pleural cavity. Malignant pleural mesothelioma is a highly invasive disease with a very long latency and treatment is rarely effective, since only few patients survive more than one year after diagnosis (Carbone et al., 2007). Asbestos, a fibrous mineral widely used throughout the 20th century, has been acknowledged to being the main causative agent (Wagner, 1979).

Although systemic chemotherapy with novel combinations of platinum-based drugs and antimetabolites showed some degree of success in selected patients, prognosis remains generally poor (Kindler, 2008; Robinson et al., 2005). The fact that the disease is often intrinsically resistant to treatment, combined with the notion that the majority of patients are elderly due to a long latency, and thus prone to complications and comorbidities, further limits treatment options (Ray, Kindler, 2009).

Malignant pleural mesothelioma is still regarded as a rare disease, despite the fact that its incidence has been steeply rising in the last decades and is not expected to level before the year 2020 (Robinson et al., 2005). Increased incidence and the fact that conventional antitumour treatment options are ineffective, highlight the need for novel therapies for MPM patients and underline the urgency for implementation of more effective diagnostic, prognostic, predictive and, nevertheless, therapeutic targets.

Thorough understanding of the differences between normal and malignant cells is crucial in the search and development of such targets. More comprehensive knowledge of tumour biology in general and malignant pleural mesothelioma in particular allows and facilitates the discovery and validation of novel potential markers. Several such potential markers can be found among proteins involved in the cellular pathways that mediate malignant transformation and, at least in part, constitute the so called hallmarks of cancer, e.g. cellular signalling, proliferation and apoptosis (Hanahan, Weinberg, 2000).

This chapter focuses on presenting survivin, a cancer-specific protein involved in both proliferation and apoptosis regulation. Furthermore, the aim of this review is to explore survivin's potential as a prognostic and therapeutic target for MPM.

2. Survivin as an interloper between apoptosis and proliferation

Hanahan and Weinberg described ten so called hallmarks of cancer and defined them as features common to all malignancies. They consist of acquired phenotypic properties, rooted in the defects of key regulatory mechanisms of cells within a tissue, namely: unlimited replication potential, self-sufficiency in growth signals and their transduction, insensitivity to growth inhibitors, resistance to apoptosis, as well as sustained angiogenesis, adjacent and distal tissue invasion, abnormal metabolic pathways, genome instability, avoidance of the immune system and chronic inflammation (Hanahan, Weinberg, 2000;2011). Among the latter, apoptosis and proliferation deregulation are at the very core of malignant transformation and have thus been given special attention in the present paper.

Apoptosis is an evolutionary conserved ATP-dependent type of programmed cellular death, executed by caspases (cysteine proteases), which lead to a progressive disruption of the cell structures and formation of membrane-enclosed vesicles, named apoptotic bodies. Apoptosis can be triggered by either intrinsic or extrinsic death signals and is regulated by two gene families, Bcl₂ and IAP (Pizem, Cor, 2003). Survivin is a member of the IAP (Inhibitor of Apoptosis Protein) family and is thus an important antagonist of apoptosis, whose biology is discussed in more detail in the present paper.

The very fact that survivin is a member of the IAP family and is structurally similar to IAPs, such as ILP-2, livin and apollon, means that initial research on this protein was focused on its antiapoptotic role (Li et al., 1998;Salvesen, Duckett, 2002). Even though a substantial body of work has been invested in elucidating survivin's role as an apoptosis inhibitor, several issues are unclear and remain a subject of discussion.

Survivin's central role is believed to be suppression of apoptosis during embryogenesis (Adida et al., 1998). Survivin inhibits apoptosis on several levels. It binds and inactivates effector caspases 3 and 7 (Pizem, Cor, 2003). Moreover, survivin inhibits apoptosis by preventing mitochondrial export of the proapoptotic protein SMAC/Diablo (Lima et al., 2009). Furthermore, survivin binds and is stabilised by the aryl hydrocarbon receptor-binding protein (AIP), which enhances survivin's antiapoptotic functions and helps elevate a cell's antiapoptotic threshold (Kang, Altieri, 2006). Another antiapoptotic function of survivin is directly connected to its promitotic functions, since the binding of survivin to mitotic spindle microtubuli inhibits a default intrinsic triggering of cellular death during mitosis (Li et al., 1998). Notably, survivin expression in cancer cells helps them overcome intrinsic and extrinsic death signals.

Following the discoveries of survivin's antiapoptotic and cytoprotective functions, it was subsequently discovered that survivin has several other functions and is actively involved in cellular proliferation (Lens et al., 2003), microtubule dynamics and cellular stress response (Fortugno et al., 2003). Survivin is thus now regarded as a multifunctional, nodal protein.

Although cellular death and cellular division seem to be directly opposite processes, they are indeed intimately related. And that relation makes perfect sense when tissue homeostasis is taken into account. Redundant, damaged or infected cells need to be removed by apoptosis, which does not damage adjacent cells, and substituted with new,

well performing ones by mitosis. Progression through the cell cycle, which allows for the production of new cells, and programmed cellular death, which causes loss of cells within tissues, share a number of control mechanisms that need to be strongly interlinked in order to assure normal tissue development and homeostasis. Several proteins are involved in the regulation of both processes. Disruption of the balance between proliferation and apoptosis is an important feature of malignant tumours and further underlines the importance of cell cycle/apoptosis regulation proteins in tumourigenesis (Hanahan, Weinberg, 2011).

Cellular proliferation, like apoptosis, is a tightly regulated process. Survivin promotes proliferation by direct binding and stabilisation of mitotic spindle microtubuli during the initial stages of mitosis (Altieri, 2010) and by regulation of chromosome segregation. Additionally, survivin is an important part of the chromosome passenger protein complex (CPP) and interacts with several CPP components, assuring their stability (Fortugno et al., 2002). In fact, Li et al. demonstrated that disruption of the survivin-mitotic spindle microtubuli interaction results in the loss of survivin's antiapoptotic function and an increase in Caspase 3 activity, a mechanism of inter-mitotic apoptosis induction (Li et al., 1998). The latter suggests, as mentioned previously, that survivin functions as an inhibitor of a default triggering of apoptosis during the G2/M phase of the cell cycle and might explain why survivin expression peaks at the transition from phase G2 to M (Beardmore et al., 2004). This means that survivin overexpression allows malignant cells to overcome proapoptotic checkpoints and favours aberrant progression through mitosis, regardless of critical genome defects, absence of growth signals or stress.

Additionally to its promitotic and antiapoptotic functions, survivin has also been demonstrated to be involved in cellular stress response pathways, interacting with the molecular chaperone Hsp90. Hsp90 is a central stress response chaperone, which helps cells to adapt to stress. Fortugno et al. demonstrated that Hsp90 binds survivin and stabilises it, meaning that the formation of such Hsp90-survivin complexes efficiently prevents apoptosis and mediates cellular proliferation, overcoming the environmental stress. Since both Hsp90 and survivin are often overexpressed in cancer, such interaction mechanisms are often exploited by cancer cells, allowing them to retain their proliferative potential, despite unfavourable environmental conditions (Altieri, 2004; Fortugno et al., 2003).

Despite the fact that new pathways involving survivin are constantly being discovered, it is fairly clear that survivin is a very important cancer gene that adjuvates the accumulation of malignant phenotype features. In sharp contrast with its vast array of functions, survivin (Baculoviral IAP Repeat Containing 5; BIRC5) is a rather small protein of 16.5 kDa (142 amino acids) and is the smallest member of the IAP family (Pizem, Cor, 2003).

Unlike other IAP family members, survivin has only one BIR domain (Figure 1), which is essential for its antiapoptotic function (Ambrosini et al., 1997). Survivin spontaneously forms antiparallelic dimers *in vitro*, but novel data suggest that a monomeric form is required for its proper functioning (Altieri, 2008b). Within the cell, survivin can be present in the nucleus, cytosol and mitochondria (Mahotka et al., 2002). Its expression levels are cell-cycle dependent, with a peak expression at the transition from phase G2 to M, which means that survivin expression reaches its highest point at the initial stage of cellular division (Beardmore et al., 2004).

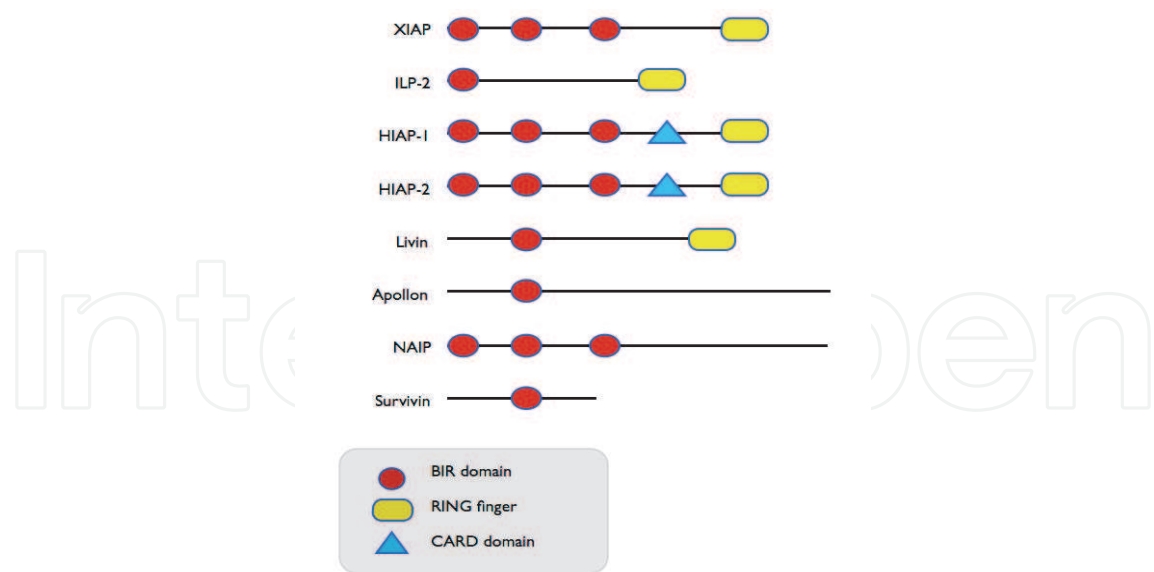


Fig. 1. Structures of IAP family proteins, adapted from (Salvesen, Duckett, 2002).

Survivin is encoded by the *BIRC5* gene, located on chromosome 17q25 in the human genome and is composed of four exons and three intons (Reed, 2001). Posttranscriptional modifications, namely alternative intron splicing, are responsible for the formation of alternative survivin isoforms (Noton et al., 2006), which are described in Table 1. The exact meaning of alternative *BIRC5* splicing is yet to be elucidated.

BIRC5 gene expression is controlled by a TATA-less inducible promoter with a canonical CpG domain and three cell cycle dependent elements (CDE) (Li, Altieri, 1999). Single nucleotide polymorphisms in the *BIRC5* promoter region and methylation of CpG domains have been demonstrated to affect *BIRC5* expression levels (Li, Altieri, 1999;Ma et al., 2010;Ma et al., 2011). The exact signals that trigger promoter activity and activate the expression of *BIRC5* are not completely understood. It is possible that tumour suppressors repress *BIRC5* expression, whereas oncogenes activate the promoter and trigger expression. Mirza et al. confirmed that wild-type p53, a crucial tumour suppressor, suppresses survivin expression (Mirza et al., 2002).

Isoform	Modification (relative to WT)
survivin-2A	none; wild type survivin isoform
survivin-2B	alternative exon 2
survivin-deltaEx-3	deletion of exon 3
survivin-3B	alternative exon 3

Table 1. Survivin isoforms, summarised from (Noton et al., 2006)

As mentioned previously, survivin is present in both the nucleus and cytoplasm. Its various subcellular localisations are inevitably linked to its distinct functions. Nuclear survivin is thought to be involved in proliferation regulation, whereas cytoplasmic survivin has an anti-apoptotic role (Stauber et al., 2007). It is believed that both survivin isoform and phosphorylation status dictate its subcellular localisation and function, but this theory has not been thoroughly researched yet (Altieri, 2010;Mahotka et al., 2002).

It should thus be noted that survivin has a unique role in the cell, providing an interplaying link between cellular death and cellular division. Both apoptosis and cellular proliferation are often deregulated in cancer and components of both pathways could be used as potential anticancer therapeutic targets.

3. Survivin in cancer

Very few potential anticancer therapeutic targets have boosted as much promise as survivin. In fact, one of survivin's most prominent features is its interesting expression pattern. Survivin is expressed in embryonal tissue and malignant cells, but is virtually absent from terminally differentiated tissues, with very limited exceptions, such as thymocytes, endothelial cells and bone marrow cells (Altieri, 2003a; Pizem, Cor, 2003; Sah et al., 2006). The almost exclusive tumour-specific expression pattern undoubtedly means that survivin has an important role in the development and progression of cancer (Altieri, 2008a). Survivin expression has been demonstrated in several types of human malignancies (Figure 2), such as medulloblastoma (Pizem et al., 2005), colorectal carcinoma (Sarela et al., 2000), lymphoma (Ambrosini et al., 1997) and many others (Nachmias et al., 2004). Klabatsa et al. demonstrated that survivin is also expressed in malignant pleural mesothelioma (Klabatsa et al., 2005).

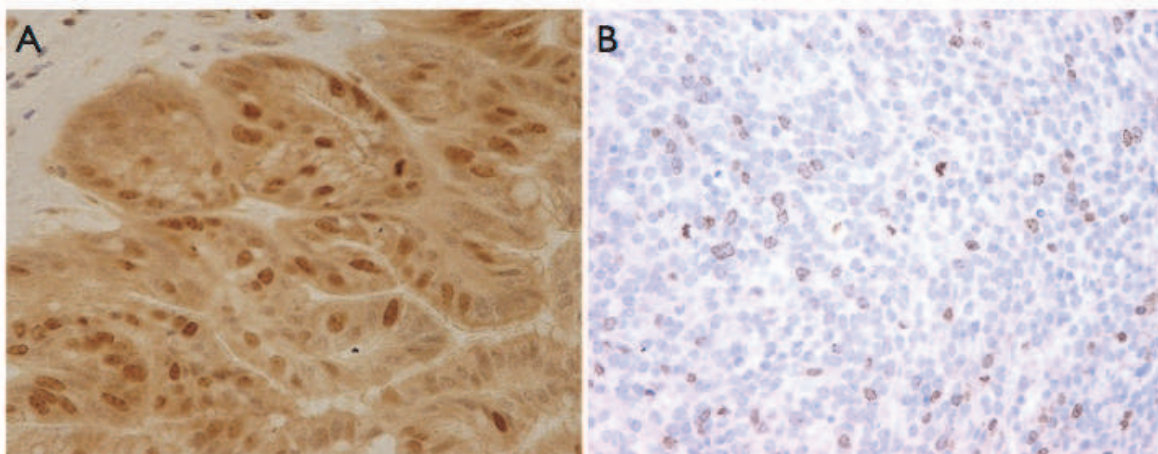


Fig. 2. Survivin expression in cancer. A: Gallbladder adenocarcinoma. B: Medulloblastoma (immunohistochemistry, 400x magnification).

Additionally to assessing survivin's presence, retrospective analyses demonstrated that survivin expression levels are linked to tumour progression and patient survival. Survivin over-expression proved to be a negative prognostic marker in several types of cancer, like colorectal (Sarela et al., 2001) and hepatocellular (Ikeguchi et al., 2002) carcinoma. On the other hand, Kennedy et al. confirmed that survivin expression is a positive prognostic marker for breast cancer (Kennedy et al., 2003). In fact, increased survivin expression correlated with more pronounced disease progression and a more aggressive phenotype, poorer response to treatment and shortened patient survival (Sah et al., 2006).

It is now generally accepted that survivin is both a negative prognostic marker and a positive predictive marker, since its expression reliably predicts response to treatment and disease progression (Kato et al., 2001). Moreover, it is possible that an increase in survivin expression might improve a tumour's response to therapy, since high-survivin tumors tend

to be more aggressive and proliferative and thus more likely to respond to cytostatic treatment (Petrarca et al., 2011; Span et al., 2006).

Besides survivin's role in cancer progression, its sharp tumour-specific expression pattern means that survivin is a promising potential therapeutic target for many types of cancer. Several preclinical and early-stage clinical studies have indeed demonstrated the feasibility and effectiveness of survivin-based anticancer treatments (Altieri, 2003b).

4. The role of survivin in malignant pleural mesothelioma

4.1 Prognostic role

As mentioned previously, a straightforward negative prognostic value for survivin has been confirmed for several types of cancer throughout a vast array of retrospective studies. But very few studies on survivin's prognostic and predictive role in malignant pleural mesothelioma have been published so far (summarised in Table 2).

Unfortunately, as Table 2 indicates, results of those studies are still conflicting. Nevertheless, it appears that survivin has a negative impact on survival of malignant pleural mesothelioma patients, although the numbers of patients included in the studies were generally low. Notwithstanding the latter, it is important to note that those studies unanimously confirmed that survivin indeed is extensively expressed in malignant pleural mesothelioma (Figure 3).

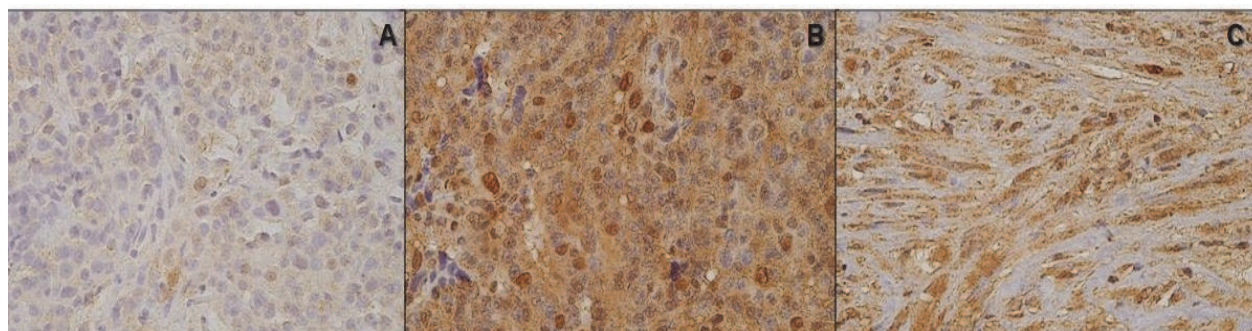


Fig. 3. Survivin expression in different histological types of malignant pleural mesothelioma. A: epitheloid histological type, B: biphasic histological type, C: sarcomatoid histological type (immunohistochemistry, 400x magnification).

As for those studies, differences in survivin detection and expression quantification methods might complicate any attempts at data comparison. But when the immunohistochemistry-based studies from Table 2 are selected and compared, striking differences are observed in the numbers of patients with survivin-positive tumours. Gordon et al. detected 76 % of survivin positive malignant pleural mesotheliomas (Gordon et al., 2007), which is in concordance with the 77 % of survivin positive malignant pleural mesotheliomas detected by (Klabatsa et al., 2005), whereas Kleinberg et al. demonstrated survivin expression in 64 % of malignant pleural mesothelioma patients included in their study (Kleinberg et al., 2007). In comparison, in our recently published paper, all (100 %) of the malignant pleural mesothelioma specimens from 101 patients analysed were survivin positive, with a median level of 67 % of survivin positive tumour cell nuclei (Hmeljak et al., 2011).

Those results, although very broad-range and seemingly inconsistent, underline a very important point: survivin is present and actively expressed in malignant pleural mesothelioma.

Authors	Year	Patients	*Methods	Correlation with survival	Reference
Klabatsa et al.	2005	32	immunohistochemistry	positive	(Klabatsa et al., 2005)
Gordon et al.	2007	66	immunohistochemistry, qRT-PCR	negative	(Gordon et al., 2007)
Kleinberg et al.	2007	77	immunohistochemistry, western blot	non significant	(Kleinberg et al., 2007)
Lan et al.	2010	44	immunocytochemistry, qRT-PCR	negative	(Lan et al., 2010)
Hmeljak et al.	2011	101	immunohistochemistry	non significant	(Hmeljak et al., 2011)

*Only patients with malignant pleural mesothelioma are included, although some of the studies comprised malignant peritoneal mesothelioma and reactive pleuritis patients.

Table 2. Overview of studies on the prognostic role of survivin in malignant pleural mesothelioma

And although its prognostic value in malignant pleural mesothelioma has not been conclusively assessed yet, survivin’s role as a potential therapeutic target should not be dismissed.

4.2 Therapeutic role

Currently, malignant pleural mesothelioma treatment is consisted of platinum-based systemic chemotherapy with several additional combinations. One of the most successful approaches is combined systemic chemotherapy with cisplatin and pemetrexed (Belli et al., 2009). Surgical resection of the tumour is possible only in selected cases, which are rare, due to the fact that most patients are diagnosed at an advanced stage of the disease, when debulking surgery becomes too dangerous (Kindler, 2008). Another important obstacle of present therapies is the fact that malignant pleural mesothelioma often develops resistance to therapeutic approaches, rendering them ineffective.

Since conventional therapies regularly fail, a surprisingly high number of novel therapeutic approaches have been recently (and are being currently) explored. Such intensive research is motivated by increasing numbers of patients and the absence of current effective therapies (Ray, Kindler, 2009). It is a pleasant surprise that such an investment is being made in the treatment of a fairly rare disease. Among those novel strategies, special attention has been devoted to antisurvivin therapies, which have been extensively tested in the preclinical setting. Survivin inhibition resulted in decreased survival of malignant pleural mesothelioma cells (Xia et al., 2002) and increased sensitivity to radiotherapy (Kim et al., 2007). Data from those studies indicate that posttranscriptional targeting of survivin increases the rates of both spontaneous and radiation-induced apoptosis and highlight the

central role of survivin in maintaining apoptosis resistance and mitotic potential of malignant pleural mesothelioma cells. Moreover, use of conditionally replicative adenoviruses containing the *BIRC5* promoter increased apoptosis in both *in vitro* and *in vivo* models of malignant pleural mesothelioma (Zhu et al., 2006).

Antisurvivin treatment approaches include not only posttranscriptional knockdown with antisense oligonucleotides or siRNA molecules. Low molecular weight chemical inhibitors, such as YM155 (Nakahara et al., 2007), and immunogenic peptides, such as survivin-2B80-88 (Tsuruma et al., 2004) are being tested in the preclinical and early-phase clinical setting for breast, lung and colorectal cancer. Promising results of such antisurvivin therapies, applied to other cancer types (Hansen et al., 2008; Olie et al., 2000; Tsuruma et al., 2008), further confirm the feasibility and effectiveness of antisurvivin therapeutic approaches for the treatment of malignant pleural mesothelioma patients.

Our group recently performed a pilot *in vitro* experiment, in which a combination of survivin knockdown by siRNA (Stealth® siRNA BIRC5HSS179403; Invitrogen, Carlsbad, CA, USA) and hypotonic chemotherapy with cisplatin (*cis*-diamminedichloroplatinum, CDDP) dissolved in ultrapure water, has been administered to mesothelioma cell line MSTO-211H. The survival of treated cells was assessed by the clonogenic assay (Figure 4). We found that the combination of survivin silencing and administration of a hypotonic solution of cisplatin very effectively reduced survival of MSTO-211H cells compared to survivin silencing only ($p < 0.001$) and also compared to survivin silencing and application of isotonic cisplatin dissolved in phosphate buffered saline ($p = 0.005$). Our preliminary results suggest that inhibition of survivin effectively reduces the survival of malignant pleural mesothelioma cells. Moreover, the effect is substantially amplified when a combined approach of gene therapy and chemotherapy with cisplatin is applied. The exact nature of the observed combined antitumour effect (whether it is additive or synergistic) was not determined in the present phase of experiments, but it should undoubtedly be interesting to assess.

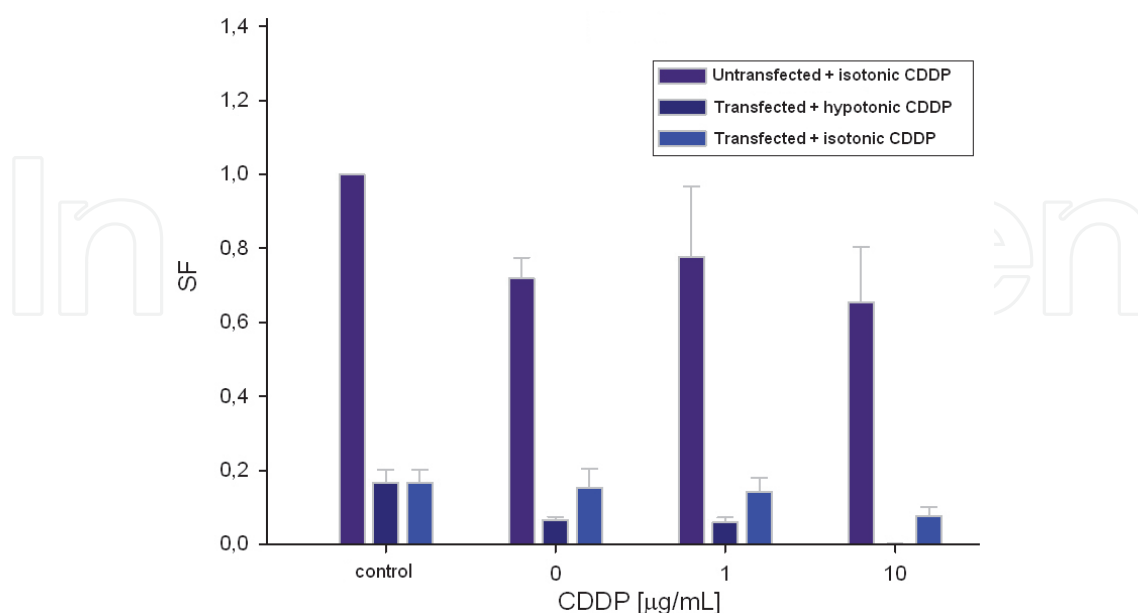


Fig. 4. Survival fractions of MSTO-211H cells after transfection with Stealth® siRNA BIRC5HSS179403 and subsequent chemotherapy with cisplatin.

Nowadays, malignant pleural mesothelioma rarely responds to conventional treatment and prognosis remains poor, despite extensive preclinical research and improvement in diagnosis. Novel, locally administered targeted therapies are promising, since pleural mesothelioma has some features that indicate the feasibility of such therapies. Surface accessibility of the tumour and predominantly local spread of the disease are characteristics that would allow successful local gene-therapy-based treatment (Albelda et al., 2009), such as antisurvivin siRNAs or antisense oligonucleotides.

Preclinical research on therapeutic targeting of survivin in malignant pleural mesothelioma has confirmed the effectiveness and feasibility of such approaches, especially when combined with existing conventional therapies and has laid a strong foundation for translation into the clinic.

4.3 Biological and ethiological role

Notwithstanding the widely acknowledged and studied presence of survivin in malignant pleural mesothelioma or its potential therapeutic value, very little is known about the actual mechanisms of activation of the *BIRC5* gene during malignant transformation of mesothelial cells. It has been suggested that activated oncogenes might trigger *BIRC5* expression, since Falleni et al. demonstrated a gradual increase in survivin mRNA from normal mesothelial cells through inflammatory pleuritis and malignant mesothelioma (Falleni et al., 2005). The latter indicates that survivin expression increases during the phases of malignant transformation and is correlated with a progressively increasing malignant phenotype. It has not, however, been elucidated, whether increased survivin expression is a cause or a consequence of malignant transformation. And even though thorough retrospective research might not manage to elucidate the value of survivin expression levels as a malignant pleural mesothelioma prognostic marker, survivin will still remain an intriguing and promising potential therapeutic target.

5. The role of survivin in malignant peritoneal mesothelioma

Although the primary focus of the present text is malignant pleural mesothelioma, the latter is not the only form of mesothelial malignancy. Malignant peritoneal mesothelioma (MePM) is a much rarer manifestation of mesothelial malignancies, accounting for 20 - 33 % of all malignant mesotheliomas (Brida et al., 2007). Although the biology of malignant peritoneal mesothelioma remains largely unclear, this form of mesothelioma is known to arise from and spreads along the peritoneal mesothelium, remaining confined to the peritoneal cavity for most of its natural history (Deraco et al., 1999). Similarly to pleural mesothelioma, malignant peritoneal mesothelioma is characterised by a poor prognosis and poor response to treatment. Conversely, the importance of novel potential prognostic and therapeutic targets is just as urgent as in pleural mesothelioma. Zaffaroni et al. demonstrated that survivin is expressed in malignant peritoneal mesothelioma and its expression is a negative prognostic marker. Moreover, the same study confirmed that survivin knockdown using RNA interference markedly decreased MPeM cell survival *in vitro* (Zaffaroni et al., 2007).

6. Conclusions

The aim of modern anticancer treatment strategies is a “clean” removal of malignant cells with limited or, preferably, no damage to adjacent normal tissues. Despite recent advances

in anticancer treatment, malignant pleural mesothelioma remains a fatal disease with an extremely poor prognosis. Several retrospective studies confirmed high levels of survivin expression in malignant pleural mesothelioma, but failed to conclusively assess its prognostic significance. On the other hand, survivin targeting proved to be an effective approach for malignant pleural mesothelioma treatment. Unfortunately, several important pieces of the survivin-mesothelioma story are still missing and a lot of research is still awaiting.

The present review only briefly explored the issue and we hope it helped pinpoint some of the missing bits of information that need to be clarified for a thorough understanding of the matter. It is our firm belief that combining survivin targeting with local or systemic conventional therapies would be a valuable therapeutic strategy for mesothelioma patients. Current preclinical data are extensive and encouraging and we can only hope that translation in the clinical setting will be prompt and successful. Malignant pleural mesothelioma is, in fact, a deadly disease and still has one of the worst prognoses among all malignancies. Research and validation of novel targets can bring new hope to patients, who often find themselves frustrated by the lack of effective treatment options. And in the case of malignant pleural mesothelioma, the numbers of those patients are increasing steeply at this very moment.

7. Acknowledgements

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8. References

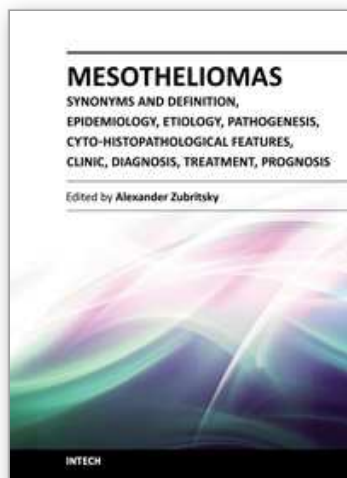
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Mesotheliomas - Synonyms and Definition, Epidemiology, Etiology, Pathogenesis, Cyto-Histopathological Features, Clinic, Diagnosis, Treatment, Prognosis

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Mesotheliomas are mysterious mesothelial tumors in that they are relatively rare, difficult to diagnose, with a large number of synonyms, and the etiology and pathogenesis of the disease are still not fully disclosed. This problem attracts the attention of various specialists in the field of medicine and biology every year. In recent years there has been a significant increase of mesothelioma morbidity in most of the countries, due to the further industrialization of society. In this regard, this book has been published with the participation of an international group of experts with rich experience from around the world . The book consists of 14 chapters containing the most advanced achievements of all aspects of the various types of mesotheliomas, both in humans and domestic animals, at a high methodological level. This book is intended for biologists and all health care workers, mostly oncologists of different profiles, as well as students of medical educational institutions engaged or even just interested in the problems of mesotheliomas.

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