REVIEW

New diagnostic and therapeutic avenues for mesothelioma

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Abstract: Mesothelioma is a rare form of cancer affecting the mesothelium lining. It is usually caused by asbestos exposure or exposure to nanofibers. Median survival is less than one year in the mesothelioma patients. Due to its severity, there is a dire necessity to find out new diagnostic and therapeutic strategies. Some recent strategies could help us in fighting against mesothelioma. Diagnostic tools include a range of biomarkers or biotechnological procedure. Therapeutic tools include chemotherapeutic strategies along with immunotherapy, gene therapy and alternative therapy.

Keywords: Mesothelioma, diagnosis, therapeutic tools.

INTRODUCTION

Mesothelioma is the cancer of the mesothelium lining, covering the lungs internally but mesothelioma can also be started from abdomen or heart internally. It is also known as Malignant Mesothelima and is a rare form of cancer. It is in study since 1870 but got its distinct cancer classification in 1960 (Yarborough, 2006). Many of the biomarkers can also become the therapeutic targets. Similarly, many of the therapeutic targets could be efficiently used for the diagnostic purposes of malignant mesothelioma. With the passage of time, there is advancement in the field of medicine for diagnosis and management of a disease (Qadir *et al*., 2006; Qadir *et al*., 2007; Qadir and Malik, 2008; Qadir and Malik, 2010a).

NOVEL DIAGNOSTIC AVENUES

Diagnosis of mesothelioma in early stages is one of the most important targets of researchers, so that the treatment could be started in the early stages.

Over expression of MUC1/EMA proteins

Researchers found that MUC1/EMA over expression occurs in most of the epithelioid mesotheliomas. So, they are of the opinion that MUC1 could be used in the diagnosis of mesothelioma. MUC1 is a type of mucin that covers various organs of the body and protects them from a large number of infections and EMA is epithelial membrane antigen. Influence of MUC1 over expression in the prognosis of mesothelioma still needs research.

Mutation of BAP1

BRCA1–associated protein 1 (BAP1) is a tumor suppressor gene and its mutation could result in increased chances of malignant mesothelioma, atypical melanocytic tumors and other neoplasms. Researchers after working on BAP1 mutations have found that mole-like melanocytic lesions could be there in the people with such mutations. So, these lesions could help in the identification of the individuals with germ line BAP1 mutations increasing chances of developing mesothelioma and melanoma in those people (Carbone *et al*., 2012).

Function of Yes protein

Yes a protein that belongs to the subfamily of Src family of kinases (SFKs) is found to have an important role in the cell growth in malignant mesothelioma. SFKs are actually non-receptor tyrosine kinases and are involved in the start or stop of many of the cellular functions. It can be used for the diagnosis of mesothelioma (Sato *et al*., 2012).

Parakeratotic-like (PK-like) cells in the effusion specimens of pleura

Cytological assay of effusion is considered as one of the most important procedure for early stage detection of mesothelioma but it is also a difficult process. In a study, researchers have found that Parakeratotic-like (PK-like) cells in the effusion specimens of pleura could become one of the important diagnostic samples for malignant mesothelioma. PK-like cells with orange cytoplasm and pyknotic nuclei are found on Papanicolaou-stained cytology slides of many of the cases specific for malignant mesothelioma (Gao *et al*., 2012).

Role of Glut-1, EMA and desmin expression

Glucose transporter 1 (Glut-1), Epithelial membrane antigen (EMA), and Desmin expression could help us in differentiation between the benign mesothelial cells and the malignant mesothelial cells. Glut-1 helps in the

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movement of glucose across the plasma membranes. EMA is found in the mammary gland epithelium and lungs and has been found helpful in the identification of some the tumors. Desmin is important in muscle cell structure.

Presence of EAAT1, GS and Dvl3 proteins

The workers have found positive staining of the mesothelioma samples for Excitatory amino acid transporter-1 (EAAT1), Glutamine synthetase (GS) and Dvl3. Dishevelled (Dvl) family of proteins are found to be linked to the cancer. These are the mediators of Wnt/beta-catenin signaling pathway in which Wnt signaling pathway is involved in taking the information from the surface of the cells to the DNA expression in the nucleus and beta-catenin regulates epithelial cell layers. EAAT1 is among the neurotransmitter transporters. GS is important for the metabolism of nitrogen. Researchers have also found that with the increased degree of staining of the samples with EAAT1, chances of survival decreased. Both EAAT1 and GS are involved in the rapid conversion of glutamate into glutamine showing that glutamine could have some important role in mesothelioma (Li *et al*., 2012).

Presence of SMRP

Serum soluble mesothelin-related peptide (SMRP), which is a blood based biomarker, could be effectively used for the detection of severity of diseases related to asbestos. They have found that the elevated levels of serum SMRP are related to the duration of the past exposure of the body to asbestos (Park *et al*., 2012).

Presence of Paraneoplastic leukocytoclastic vasculitis

Paraneoplastic leukocytoclastic vasculitis could represent malignant pleural mesothelioma in advance. Vasculitis is usually found to be linked to malignancies and research has attributed Paraneoplastic vasculitis to lung cancer. Leukocytoclastic vasculitis is a type of skin lesions in many of the patients. These are mostly present on legs and accompanied by fever (Wong *et al*., 2012).

Presence of proteins belonging to the Wnt family

The proteins belonging to Wnt family could help in making an opinion about malignant pleural mesothelioma. Wnt family of proteins are involved in a variety of bodily functions such as embryonic development and cell differentiation. It includes Wnt1, Wnt2B and Wnt5A, which are also found to be involved in carcinogenesis. Among these proteins, Wnt2B expression is found to be more than the Wnt1 and Wnt5A in malignant pleural mesothelioma. Researchers also found that the increase in Wnt2B expression results in lower overall survival. This protein is also related to survivin a protein disturbing the programmed cell death and c-Myc-regulator gene causing cell proliferation in many cancers expression (Kobayashi *et al*., 2012).

Diagnosis on the basis of keratin statins, Hematoxylin-eosin examination and homozygous p16 gene deletions

Keratin statins, Hematoxylin-eosin examination and homozygous p16 gene deletions could potentially help us in distinguishing between the benign from the malignant mesothelial proliferations. Desmoplastic mesotheliomas have descending production of keratin-positive spindled cells between S100-positive fat cells. Moreover, due to different pleura than normal malignant mesothelioma Hematoxylin-eosin stain can help us in its detection. Researchers have also reported that mesotheliomas often represent homozygous p16 gene deletions Fluorescence in-situ hybridization on tissue sections can help in the detection of these deletions. This technique is used to detect the presence of absence of DNA sequences on chromosomes (Churg *et al*., 2012).

Pleural fluid DNA integrity index

Pleural fluid DNA integrity index could also potentially help us in the identification of mesothelioma by considering the malignant pleural effusions. DNA integrity index refers to the ratio of the longer fragments of DNA to the shorter fragments of DNA and it has been found that the DNA released from malignant cells has different size as compared to the DNA released from the normal cells. Pleural fluid DNA integrity index in malignant pleural effusions is high as compared to the benign effusions (Sriram *et al*., 2012).

Biopsy

Ultrasound-guided cutting needle biopsies have been found to be among the optimal techniques for the diagnosis of malignant pleural mesothelioma (Stigt *et al*., 2012).

Over expression of zeb1 and TWIST1 proteins

Malignant mesothelioma can be distinguished from the lung adenocarcinomas and metastatic adenocarcinomas by checking for the over-expression of Zinc finger E-box-binding homeobox 1 (zeb1) and Twist-related protein 1 (TWIST1). Zeb1 is involved in the inhibition of interleukin-2 (IL-2) gene expression and TWIST1 is involved in cell lineage determination and differentiation. Zeb1 and snail family of transcription factors could also help in the differentiation of biphasic mesothelioma from epithelioid and sarcomatoid mesotheliomas as biphasic mesothelioma shows more expression of these.

Presence of NLRP1

Workers after working on Italian patients found that not all type of Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing proteins (NLRP) are involved in mesothelioma but NLRP1. This protein is more commonly found in patients of mesothelioma. So, this protein could help us in the diagnosis of mesothelioma. While NLRP3 has no significant role in the mesothelioma (Pontillo *et al*., 2012).

Absence of NF2 gene

Working on the heterozygous loss of NF2 gene a gene producing Merlin protein that is a tumor suppressor can also help us in the early diagnosis of mesothelioma as this process has been found to be the initial step in molecular alteration in malignant pleural mesothelioma and well-differentiated papillary mesothelioma of the peritoneum (WDPMP) (Nemoto *et al*., 2012).

Protein biomarkers

Workers have found 13 protein biomarkers that could be used for early detection of malignant mesothelioma in asbestos-exposed population. These proteins include Apo A-1, C9, Ck-b-8-1, CDK5/p35, BLC, Coagulation Factor IX, FCN2, Fibronectin, sICAM-2, SCF sR, Midkine, Kallistatin and CD30 (Ostroff *et al*., 2012).

Presence of fibulin-3

There is four to five times higher level of a plasma protein, fibulin-3, in the patients of mesothelioma as compared to the patients of other tumors in the chest or asbestos exposed patients. This protein has been found around the outside cells and free floating in the blood plasma and extracellular fluid (Pass *et al*., 2012).

NOVEL THERAPEUTIC AVENUES

The emergence of resistance and tolerance to the existing drugs has created a decreased efficacy of these drugs in use. This problem has been tried to be overcome by increasing the drug delivery to the target site by the use of polymers (Khalid *et al.*, 2009; Hussain *et al.*, 2011) or through nanotechnology (Naz *et al.*, 2012; Ehsan *et al.*, 2012), synthesis of new drugs, either by the use of proteomics (Qadir, 2011; Qadir and Malik, 2011), or synthesis from lactic acid bacteria (Masood *et al.*, 2011), or marine microorganisms (Javed *et al.*, 2011). However, now a days, the trend is being changed from synthetic drugs to the natural drugs either from plants or microbes to control the diseases (Iqbal *et al.*, 2014). The natural products are constantly being screened for their possible pharmacological value particularly for their analgesic (Parveen *et al.*, 2014) anti-inflammatory (Qadir, 2009), hypotensive (Qadir, 2010), antihyperlipidaemic (Ahmad *et al.*, 2012) hepatoprotective (Ali *et al.*, 2013; Mallhi *et al.*, 2014; Saleem *et al.*, 2014a; Qadir *et al.*, 2014), hypoglycaemic (Nisa *et al.*, 2009; Qadir and Malik, 2010b; Qadir *et al*., 2013), amoebicidal (Asif and Qadir, 2011), anti-fertility, cytotoxic (Saleem *et al.*, 2014b), antibacterial (Amin *et al*., 2012; Azam *et al*., 2013; Saleem *et al.*, 2014c), anti-viral (Ali *et al*., 2012; Aslam *et al*., 2012; Janbaz *et al*., 2013) spasmolytic (Janbaz *et al.*, 2014), bronchodilator (Janbaz *et al.*, 2013a), antioxidant (Janbaz *et al.*, 2012), anti-diarrheal (Janbaz *et al.*, 2013b), and anti-cancer (Ali *et al*., 2013a & b; Saleem *et al.*, 2013) properties. Many therapeutic strategies have been worked on to treat mesothelioma.

CTGF as a potential target

Targeting the connective tissue growth factor (CTGF), which is involved in many of the cellular biological processes, could lead to potential therapeutic strategy for malignant mesothelioma. They have observed that the elevated TGF-β pathway and the suppressed Hippo signaling pathway are among the mechanisms involved in the malignant mesothelioma. TGF-β pathway is involved in cell growth and cell differentiation while Hippo signaling pathway controls cell proliferation and apoptosis (Fujii *et al*., 2012).

Suppression of yes protein

The suppression of Yes resulted in the inhibition of the growth of cells in malignant mesothelioma through G1 cell cycle arrest and somewhat through cell death. Yes has also found to be related to the β-catenin signaling i.e. inactivation of Yes causes inactivation of β-catenin signaling resulting in the decrease of cyclin D that plays an important role in G1-S transition in the cell cycle (Sato *et al*., 2012).

Combination chemotherapy with cisplatin and pemetrexed

Malignant mesothelioma has fewer therapeutic options but combination chemotherapy, such as cisplatin along with pemetrexed, is found to be the optimal therapeutic strategy for mesothelioma (Green *et al*., 2007). This combination of drugs is also found to be the optimal combination for mesothelioma in progression (Bearz *et al*., 2012). However, with the combination of novel approaches, we would be able to increase the survival time of the mesothelioma patients or completely cure them.

Further therapeutic strategies are needed as in one study researchers have found that the outcomes of the pemetrexed based chemotherapy could be different in different patients. Previously, researchers found that the drug blocks thymidylate synthase (TS) enzyme, which is important for cancer cells to replicate their DNA, and the low levels of TS in any tumor could lead to the decreased therapeutic response to pemetrexed. Now, they have found that the drug's outcome in patients are not only affected by the low levels of TS but also by the elevated levels of folylpoly-γ-glutamate synthetase (FPGS) enzyme, which plays significant role in the survival of proliferating cells. This research also showed the increased efficacy of the drug in the presence of FPGS enzyme that helps the drug to work for longer time in the cells against TS (Christoph *et al*., 2012). Moreover, cisplatin that is considered as an effective anti-cancer drug in this case, give response in only 20% of the patients with diffused malignant mesothelioma (DMM) (Yamashita *et al*., 2012).

Effective use of cetuximab

Not only this combination but cetuximab that is an anti-epidermal growth factor receptor antibody, which is a hybrid type of mouse-human antibody, has also been found to play an effective role in the treatment of malignant pleural mesothelioma. Epidermal growth factor receptor (EGFR) is the cell surface receptor working in cell death, cell proliferation and motility, and the formation of blood vessels. Researchers have found the over-expression of this receptor in malignant pleural mesothelioma. Moreover, researchers have found the increased activity of this antibody with the addition of interleukin-2, a protein that is involved in the activity of white blood cells (Kurai *et al*., 2012). Scientists are of the view that combination of the conventional agents such as cisplatin with cetuximab, we can improve the survival time of the patients with malignant mesothelioma (Surmont *et al*., 2012).

Effective use of cixutumumab

In another study, researchers have found that cixutumumab, a humanized monoclonal antibody, works effectively against mesothelioma and this efficacy is dependent on the insulin growth factor-I receptor (IGF-IR) sites per cell (Kalra *et al*., 2012). IGF-IR is expressed at mRNA and protein level in all mesothelioma cells. It induces the biological action of insulin-like growth factor (IGF) such as IGF-I and IGF-II, which are very similar to insulin in sequence. IGF pathway is also found to play an important role in rapid increase of cancer cells and the resistance to antineoplastic treatments (McKian *et al*., 2009). On the other hand, the relation of IGF-IR sites per cell with cetuximab needs further research.

Use of histone deacetylase inhibitors

Another class of anti-cancer agents is Histone deacetylase inhibitors (HDACIs) that is found to work effectively against mesothelioma. This class includes vorinostat (suberoylanilide hydroxamic acid [SAHA]) and Valproate. Through the placebo-controlled, randomized phase III study of oral SAHA researchers have found that it works even in patients of mesothelioma in which the treatment with pemetrexed has failed (Krug *et al*., 2006). In one of the studies, it has been found that valproate in combination with doxorubicin is potent against malignant mesothelioma (Scherpereel *et al*., 2011).

Understanding MUC1/EMA glycoproteins

Utilizing the abilities of MUC1/EMA could help in the treatment of many types of mesothelioma. Variable number tandem repeat (VNTR) region containing MUC1 gene product has been found 32 times higher in mesothelioma as compared to normal cells. Understanding the mechanism of this over expression could help in eradication of mesothelioma.

FAX family of proteins could be potential therapeutic targets

Some of the FOX family of proteins including FOXO3a and FOXM1 could be potential therapeutic targets for malignant mesothelioma. FOXM1 is found to have a significant role in oxidative stress, cancer and aging by helping in the cell cycle. It is a redox-responsive transcription factor and is an important therapeutic target in solid malignancies. Although, antioxidants inhibit the expression of FOXM1 proteins but the mechanism needs further work (Newick *et al*., 2012). Researchers have found that the combination of Mito-carboxy-proxyl and Mito-TEMPOL with thiostrepton or other chemotherapeutic agents could be the optimal combination therapy for malignant mesothelioma. Mito-carboxy-proxyl is a mitochondria-targeted nitroxide that helps in the inhibition of peroxide-induced oxidative stress. TEMPOL are composed of piperidine nitroxides that have anti-oxidant properties and Mito-TEMPOL is the derivative of TEMPOL that attacks the oxidants while caring for the mitochondria. Both Mito-carboxy-proxyl and Mito-TEMPOL inhibits Forkhead box protein M1 (FOXM1) expression and stimulates redox homeostasis affecting the malignant mesothelial cell viability.

Wnt family of proteins could be the potential targets

Wnt family of proteins is sometimes over-expressed in mesothelioma. Some of these proteins such as Wnt1, Wnt2B and Wnt5A could be used as potential targets for the treatment (Kobayashi *et al*., 2012).

T-cell recovery could help us in progress against mesothelioma

Concentrating on T-cell recovery especially increase in CD8+ T-cell proliferation after one treatment period with chemotherapy for mesothelioma could be used to check whether the patient's chances of survival will be increased or not (McCoy *et al*., 2012). This research also showed that concentrating on CD8+ T-cell proliferation while receiving treatment could help to optimize the treatment.

Genetic factor could be considered in therapeutic strategies

Considering an optimal combination for the patient of mesothelioma is also the factor of genetic changes. Researchers have found that the DNA repair gene polymorphisms, especially XRCC1 Arg399Gln, resulted in reduction of the overall survival of the patients although they were receiving gemcitabine-platinum combination chemotherapy (Nina *et al*., 2012). Gemcitabine has been found to work against cancer by inhibiting the DNA methyltransferase (DNMT) activity and potentially destabilizing the DNMT1 protein resulting in the inhibition of cellular differentiation and normal development in organisms. Combination of gemcitabine-platinum has been found to be the efficient and well-tolerated treatment strategy for cancerous activities such

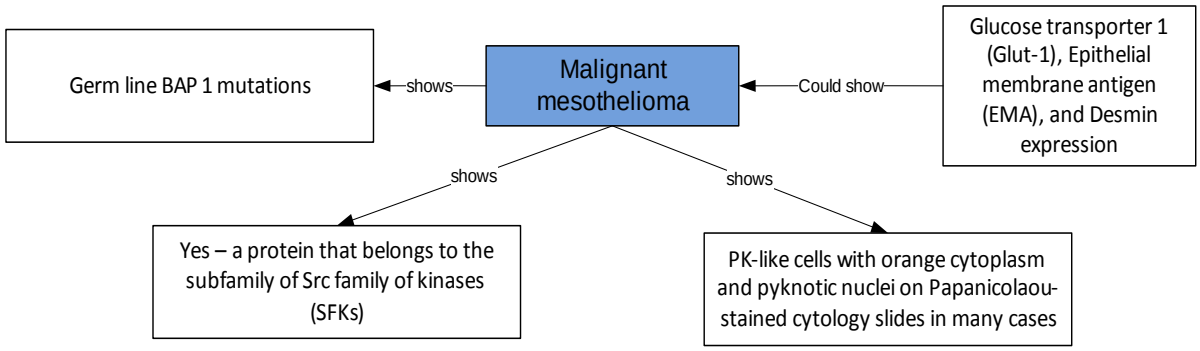

Fig. 1: Biomarkers for malignant Mesothelioma

as recurrent epithelial ovarian carcinoma (Villella *et al*., 2012). Genetic effects on other combination of drugs for the treatment of the patients of mesothelioma need more researches.

Alternative therapy with polyphenol epigallocathechin-3-gallate in green tea

On the other hand, alternative therapies could help us in potentiating our fight against mesothelioma. In one of the reviews, researchers have reported that green tea is helpful in inhibiting some of the lung cancers such as small-cell lung cancer, non-small-cell lung cancer, and mesothelioma. Researches further supported the work by finding that Polyphenol epigallocathechin-3-gallate (EGCG) found in green tea is helpful in protecting against malignant mesothelioma (Ranzato *et al*., 2012). Continuation of the efficacy of this molecule along with the other agents such as other chemotherapies can be checked for its work. EGCG is an anti-oxidant and its effects on FOXM1 protein need research to the best of our knowledge.

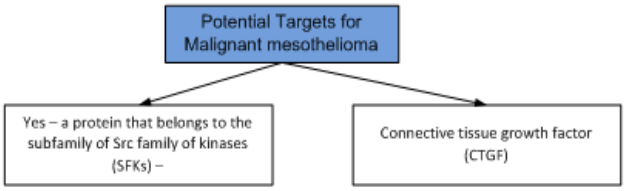

Fig. 2: Potential Targets for Malignant Mesothelioma

Alternative therapeutic strategy with Withaferin A

In another study, researchers have found that Withaferin A (WA), a compound found in the Indian medicinal plant *Withania somnifera* (also known as "Ashwagandha", or "Indian ginseng") is helpful against mesothelioma along with inflammation and angiogenesis. Researchers have found that WA works by inhibiting proteasome activity and elevating the apoptotic process in malignant pleural mesothelioma by increasing the levels of ubiquitinated proteins and pro-apoptotic proteasome target proteins (p21, Bax, IκBα). Proteasome is a complex of proteins involved in the degradation of the injured proteins. Inhibition of its activity in cancerous cells resulted in damage of cells. Just like Quercetin, WA also upregulated the Bax protein and resulted in cleavage of PARP. It also activates the pro-apoptotic p38 stress activated protein kinase (SAPK) and the expression of cell cycle and apoptosis regulatory protein (CARP)-1/CCAR1, a novel transducer of cell growth signaling along with the suppression many of the metastasis-promoting genes including c-myc (Yang *et al*., 2012). WA along with cisplatin still needs work. Not only has this but the effect of WA along with Qu also needs research.

Understanding the decreased amount of α-tocopherol, β-carotene and ascorbic acid

In one of the studies, researchers have found that the decrease in the amount of α-tocopherol, β-carotene and ascorbic acid in the body could increase the risk of getting malignant pleural mesothelioma. Moreover, the patients of malignant pleural mesothelioma have the lowest level of these anti-oxidant vitamins in the body (Emri *et al*., 2012).

Gene therapy utilizing virus

Researchers have also reported that use of adenovirus type 5 (Ad5) and fiber-substituted conditionally replicating adenovirus (CRAD) Ad5/F35 vectors for gene therapy of malignant mesothelioma. Adenoviruses are about the size of 90-100nm and many of them are responsible for the upper respiratory tract infections in children. They are used by many researchers for the transport of genetic materials. Researchers modified the E1 gene of these viruses which is controlled by human midkine promoter to make adenoviruses – Ad5F35/MKp-E1 and Ad5/MKp-E1. They found that these viruses caused oncolysis of malignant mesothelioma cells (Gotoh *et al*., 2012).

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