Asian Journal of Biology

5(3): 1-11, 2018; Article no.AJOB.39869
ISSN: 2456-7124

Potential Strategies in Treating Tumours

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Authors' contributions

This work was carried out in collaboration between all authors. Authors VNK and SM designed the study and wrote the first draft of the manuscript. Authors JM and SC managed the analyses of the study. Author TS managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJOB/2018/39869
Editor(s):
(1) Vanessa da Silva Carrara, Department of Pharmacy, State University of Maringa, Brazil.
Reviewers:
(1) Nishitha Thumallapally, Staten Island University Hospital, USA.
(2) Alessandro Poggi, Integrated Oncological Therapies, Policlinico San Martino, Molecular Oncology and Angiogenesis Unit, Italy.
(3) Philippe Groux, Switzerland.
(4) Daisy Machado, UNICAMP, Brazil.
Complete Peer review History: http://prh.sdiarticle3.com/review-history/23967

Mini-review Article

Received 4th January 2018
Accepted 11th March 2018
Published 5th April 2018

ABSTRACT

Cancer, an absolute sickness exemplified merely by uncontrolled cell proliferation, has always been a concern for universal well-being. The recurrence of cancer is, in fact, mounting globally and fatality rate resulting from this malady is markedly high. Besides genetic alterations, epigenetic modifications also play a vital role in Cancer advancement. Advancements in genomics and proteomics studies enabled researchers to search potential drug targets leading to molecular therapeutics, for instance, Atezolizumab, Nivolumab, Pembrolizumab. This article discusses the potential role of some approaches in treating tumours such as free Hyaluronidase, Hsp90 Inhibitors, Liposomes, Anti–Angiogenesis agents, Apoptosis Proteins Inhibitors, Histone deacetylases inhibitors, Nanomedicine, Blockade of PD-1/PD-L1 pathway.

Keywords: Cancer; proliferation; molecular therapeutics; anti-cancer drug.

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1. INTRODUCTION

Cancer, a sickness portrayed by uncontrolled cell proliferation in addition to differentiation, remains an overall general worry of wellbeing [1]. The frequency of cancer is, in fact, escalating globally and in spite of the notable breakthroughs accomplished with regard to cancer treatment, the fatality rate resulting from this malady is extremely high [2]. A tumour is caused by exogenous elements, including tobacco, infectious organisms, undesirable eating regimens, and endogenous factors, such as acquired hereditary transformations, hormones, and immune conditions. Such factors may act in a show or in arrangement to coordinate this multifactorial problem, and because of this intricacy of this association; at least ten years frequently go between an introduction to external factors and location of growth [3,4]. Cancer progress is not limited to the genetic changes acknowledged above, but may also involve epigenetic modifications [5]. However, not all tumours have the competence to metastasize to different areas of the body by means of lymph or blood. Malignancies could be of different sorts, for example, cervical, ovarian, breast, lung, blood, and prostate diseases and numerous others [6]. Tumours generated in specific organs exhibit diverse features of Clinical prognosis, biologic behavior, sensitivity to treatments, and therapeutic targets and tumours from other organs share crucial features in respect to oncogenic changes and tumour microenvironments of critical significance for disease treatment [7]. Surgery, Chemotherapy, Immunotherapy, and Radiotherapy are considered to be one of the most effective Cancer treatments till date. However, several limitations are also associated with these approaches [8]. As a result, there is an immediate need to find effective therapies to tackle cancers. Detection of unique cytotoxic compounds has really encouraged for the successful development of anti-cancer therapeutics. Advancements in research in molecular biology, genomics and proteomics have provided directives for the generation of potential relevant drug targets. This process has transformed the overall paradigms related to anti-cancer drug discovery, leading to the discovery of the molecular therapeutics [9].The massive enhancement of knowledge accomplished during the last year based on cancer genomics has transformed most of our understanding of cancer and have certainly offered a variety of lucrative treatment solutions. The current approaches, however, are not achieving anticipated potency in curing or perhaps even chronicity, and only an innovative update in our vision related to cancer would permit the world to contend with overall the rising knowledge of its intricacy [7]. This article discusses the potential role of some approaches in treating tumours.

2. APPROACHES IN CANCER THERAPY

2.1 The Potential Role of Mesenchymal Stem Cells (MSCs) in Cancer Therapy

Drug delivery could possibly be enhanced merely by manipulating the stromal compartment. This strategy can offer a way to deliver the medication very efficiently. The development of chemoresistance with regards stromal cells is absolutely nil. Protumorigenic stromal microenvironment can possibly be ruined by modifying their behavior. This is possible because MSCs originate away from a tumour. This strategy could be incredibly powerful road to get rid of metastasis. In order to accomplish this, comprehensive knowledge of the MSCs biology is essential, consisting of *in Vivo* mechanisms and in what way influence is being made on tumour behavior that in fact inevitably lead us to draw conclusions [10].

2.2 Role of Endorphins

As a result of certain circumstances in our body, the anterior pituitary secretes endorphins, also known as endogenous opioids.Stress is believed to be one of the causes for the onset of cancer. Discharge of inflammatory mediators like Tumour Necrosis Factor α (TNF-α), Interleukin 1 β (IL-1 β), and Interleukin 6(IL-6) (induced by catecholamine) and cortisol induce stress. Endorphins are naturally regarded as an immune booster, euphoric as well as analgesic. The immune booster nature has the ability to fight cancer without any negative effects and it has been proved in research. It acts against cancer cells by activating immune cell macrophages and NK Cells. Along with that it also liable for the discharge of dopamines in addition to substance P need to be viewed for prospective prognostic and therapeutic purpose[11].

2.3 Free Hyaluronidase for Cancer Therapy [12]

In cancer therapies, Hyaluronidases are utilized basically as spreading factors for cytotoxic

chemotherapy [13]. Drug penetration possibly be enhanced by simply bringing down the Interstitial Fluid Pressure only by degrading Hyaluronic acid by using Hyaluronidases [14]. Previous facts indicating that administration of Hyaluronidase to cancerous tissues minimizes overall the Interstitial Fluid Pressure contained in the tumours in a non-linear concentration-dependent way [15-17]. In *vitro* as well as *in vivo* breast cancer models, it has been proven that pretreatment with the use of bovine testis-derived Hyaluronidase significantly enhanced the penetration as well as the action of the oncolytic drug Adriamycin [18], and certainly generates selective Melphalan enrichment in dangerous melanomas implanted in nude mice [19].

Hyaluronidase facilitates the penetration of nanosized structures, for example, liposomal Doxorubicin into the tumour cells [20] and a particular oncolytic adenovirus ICOVIR5 [21], boosting the overall efficaciousness of the treatments in both the scenarios. Hyaluronic acid works extremely well as an additive in chemotherapy as well as in radioimmunotherapy. To deliver the 125I-named TP-3 monoclonal antibody against an osteosarcoma-associated antigen, Hyaluronidase put to use as an adjuvant [22,12]. *In vitro*, Hyaluronidase moreover reinforces the cytotoxicity of anticancer medications [23].

2.4 Potential Hsp90 Inhibitors [24,25,26]

A chaperone protein titled as heat shock protein 90 (Hsp90) is reputed for diverse functions include assisting in stabilizing proteins against heat stress, believed to fold proteins efficiently in addition to aids in protein degradation.The primary reason Hsp 90 inhibitors are explored as anticancer drugs is due to the fact that balances out various proteins essential for tumour development. A 90 kiloDalton protein, Hsp90 is likely to be the most typical heat-related proteins [27].

The major goals and objectives of Hsp90 include a role in cell signaling, protein folding, as well as tumour repression and this protein was in fact primarily isolated from stressed cells [28,29,30]. There is an absolute necessity to inhibit Hsp90 because it stabilizes proteins necessary for the vitality of cancer cells. Radicicol and Geldanamycin are Natural Hsp90 products and 17- N- Allylamino-17-demeth-oxygeldanamycin 17AAG) are semisynthetic derivatives. About 23 Hsp90 inhibitors have been reported till date [30, 31, 32].

The inhibition of Hsp90 action drives in neutralizing cellular signaling all sorts of diverse oncogenic pathways. A multitude of blockers related to Hsp90 are presently going through clinical investigation along side new agents in association with unique mechanisms which are persistently being pointed out for their function as potential anti-cancer agents [27].

2.5 Personalized Medicine

To differentiate affected individuals into possible responders as well as nonresponders and also to select patients who most certainly seem to be much less prone to endure reactions, biomarkers and more than that Gene-expression analysis can possibly be performed. This method could possibly assist physicians to detect which promoted drugs can certainly help particular patients. Clinical trials in a similar way can very effectively be rushed to make certain that nonresponders typically are not introduced to meaningless medications. Genes exclusively expressed during most cancers, for instance, PEG-3 (Parentally Expressed Gene), can enhance the cancer imaging which can result in mounting the opportunity of early finding [33].

2.6 Role of Liposome-mediated Therapy

Liposomes have changed cancer treatment by their expansive clinical applications. Liposomes regarded as carriers that present the drugs at site-specific targets and certainly improve the bioavailability as well as the stability of the drugs. Some liposome-based medications are experiencing research, in addition, to clinical trials. These are generally recognized as nanocarriers-based drug delivery platforms [34].

Liposomal doxorubicin (Myocet), liposomal cytarabine (Depocyt), liposomal daunorubicin (DaunoXome) and liposome-PEG doxorubicin (Doxil/Caelyx) are classified as accessible liposomal cancer therapeutics [33]. Doxorubicin is considered to be linked to Cardiotoxicity can possibly be reduced using a technique called PEGylation which generally involves adding polyethylene glycol onto the surface of a given liposome [35].

Research is being conducted to make liposomes more stable to hold an array of drugs and to

carry at target tumour cells thus enhancing performance and as well as risk management. Monoclonal Antibodies tagged along with Doxorubicin examined *in vivo* revealed enhanced performance when compared with untagged liposomes [35].

2.7 Role of Anti–Angiogenesis Agents

The notion of angiogenesis illustrates the formation of new blood vessels inside a tumour. In an effort to participate in metastasis, the tumour makes use of the newly formed vessels for its nourishment. Organism's typical coagulation program is altered for the growth of the tumours that in fact inevitably drives to a wide range of coagulation disorders described as coagulopathies in affected persons. The anti-cancer agent manages efficiently when the angiogenesis process is completely shut down [36].

Transmembrane receptor tissue factor is found in two isoforms specifically full-length tissue factor and alternatively spliced Tissue factor tend to form a complex with factor VII a that guides in angiogenesis of a tumour. In this way, it behaves as a determinant of a tumour [37,38,39]. The inhibitors of Angiogenesis and their mode of action are given in Table 1 [9].

2.8 Inhibitor of Apoptosis Proteins (IAPs)

Inhibitors of Apoptosis proteins assume a prominent role in Cancer progression involving in proliferation, signal transduction cascades regulating apoptosis, survival of cells and relocation of Cancer Cells. The Concept of consolidating the traditional drug approaches with anti- Inhibitor of Apoptosis Proteins has immense promise for the future treatment [48]. Anti-Inhibitor of Apoptosis Drugs mentioned in Table 2 [48].

2.9 Apigenin in Cancer Therapy

Apigenin is typically a flavonoid naturally present in the Plants. It is regarded as the low toxic compound and plays a significant role in several ways. Apigenin performs antitumor activities by various signaling pathways, that includes PI3K/AKT, AMPK, MAPK/ERK, NF-kB, JAK/STATs, Wnt/β-catenin, and JNK [70]. Anti-cancer effects of apigenin and the principal signaling pathways involved are provided in Fig. 1 [70].

All evidence accumulated up to this point evidently shows that apigenin has solid anticancer properties against different human tumours alone and in the mix with other chemotherapeutic drugs and apigenin treatment can associatively cause multiple anti-cancer effects in the same treatment [70].

2.10 Histone Deacetylases (HDAC) Inhibitors

Deregulation of DNA methylation and posttranslational histone modifications is deemed as a characteristic feature of human cancer and principally histone acetylation, which has a lethal consequence of gene transcription-deregulation [5]. Genetic alterations are not able to draw conclusions about Carcinogenesis and epigenetic processes like DNA methylation, histone modifications, and non-coding RNA deregulation [71].

Epigenetic alterations are in general reversible but genetic alterations are not. Therefore, drugs acting against epigenetic targets called epidrugs have been developed, where some of them have been affirmed for selective cancer indications, hence approving the idea of epigenetic treatment [72]. Histone deacetylases (HDAC) inhibitors provoke arrest of cancer cell cycle, differentiation, and cell death. Moreover, they lessen angiogenesis and alter immune response [71].

HDACs could play a considerable role in tumour onset and progression by altering expression and can be used as attractive candidate targets for anticancer drugs and therapies. Till now various synthetic and natural compounds have been identified that are able to hinder the activity of class I, II, and IV HDACs [5]. TSA, SAHA, and MS-275 are proved as very efficient anticancer agents verified in a wide range of hematological and solid tumour cell lines, and in experimental animal models [5]. These inhibitors exhibited the potential activity of an antitumor and no apparent toxicity in animal models [73].

2.11 Nanomedicine

Nanomedicine possesses a potential therapeutic application because of its imaging applications alongside it really has the capability for early detection of cancer, in addition, it is well known for active/passive targeting, bioavailability, and certainly biocompatible over orthodox therapies [74]. Chemotherapeutic medications usually are hydrophobic and certainly results in poor

aqueous solubility and as well as low bioavailability [75]. It may prevail over merely by nanocrystals, albumin-based nanoparticles, Liposome formulations, polymeric micelles, cyclodextrin in addition to chitosan-based nanoparticles [76]. Nanotherapeutics provides some kind of exceptionally essential strategy to overcome the lack of selectivity, multidrug resistance and moreover it drives nanoparticles that specially target the malignancy cells and certainly assists in surgical resection of tumours, and upgrades overall the remedial stability radiation-based along with other anti-cancer management modalities [75].

Table 1. Angiogenesis inhibitors and their mode of action as an anticancer agent [9]

Sl. no	Angiogenesis inhibitor	Mode of action	References
1	DLαDifluoromethylornithine	Inhibition of ornithine decarboxylase (ODC) and blocks angiogenesis	[40]
2	Angiostatin K13	Inhibitor of endothelial cell growth and angiogenesis.	[41]
3	Genistein	Down-regulates the transcription of genes involved in controlling angiogenesis.	[42]
4	Fumagillin	Inhibitor of endothelial cell proliferation and angiogenesis.	[43]
5	Endostatin	Inhibits endothelial cell proliferation; Potent inhibitor of angiogenesis and tumour growth as well.	[44]
6	(±)Thalidomide	Inhibits biosynthesis of tumour necrosis factor α (TNFα);inhibits angiogenesis.	[45]
7	Staurosporine	Blocks angiogenesis by inhibition of upregulated VEGF expression in tumour cells.	[46]
8	Minocycline	Inhibits endothelial cell proliferation and angiogenesis.	[47]

Table 2. Anti-inhibitor of apoptosis drugs [48]

Inhibitor of Apoptosis Protein (IAP)	Drug	Mode of action	Reference
XIAP	Embelin	Small molecule targeting BIR3 domain	[49,50]
	Arylsulfonamides (TWX006, TWX024)	Small molecule targeting BIR2 domain	[51]
	Polyphenylureas / Xantags	Small molecule targeting BIR2 domain	[52]
	AEG35156	Antisense	[53]
Survivin	AICAR	Small molecule targeting Hsp90	[54]
	Shepherdin	Small molecule targeting Hsp90	[55,56]
	Anti-SurvivinAb	Antibody	[57]
	LY2181308	Antisense	[58,59]
	YM155	Small molecule antagonist	[60]
cIAPs and XIAP	Compound C	Smac mimetic	[61]
	JP-1201		[62]
	Compound 11		[63]
	LBW242, LCL-161		[64]
	AT-406		[65]
	Compound 8, BV6, SM-122, SM-164		[66]
	AEG40826 (HGS1029),		[67]
	TL32711 (Birinapint)		[68]
	Compound A		
	Compound 3		[69]
	AEG40730		[67]

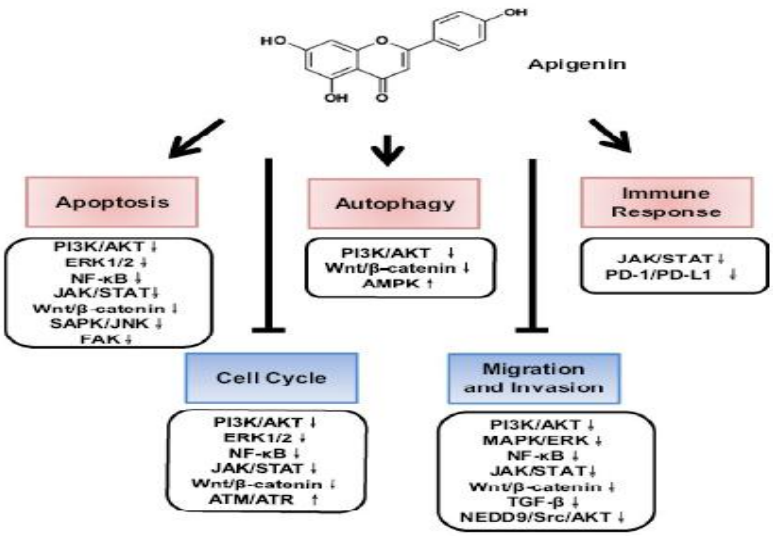

Fig. 1. Anti-cancer effects of apigenin and the principal signalingpathways [70]

Source: Xiaohui Yan et al., (2017)

Fig. 1. Apigenin prompts cell apoptosis, autophagy, in addition to immune response as well as halts cell cycle progress and cell migration and certainly invasion simply by targeting multiple signaling pathways. Bold arrows of ↙symbolizes induction and ⊥indicate suppression effects. Light arrow ↑ indicate upregulation and ↓ represent downregulation of molecular pathways

The principle concept that nanomedicine objective is to enhance so far overall the therapeutic index of anticancer simply just by transforming their pharmacokinetics as well as tissue distribution to further improve delivery to the site of action is truly acknowledged and actually has also been confirmed clinically and also future prospects with regard to nanomedicine are searching towards delivering the next generation of drugs molecularly specified agents, toxins like agents which typically motivate cell death, DNA/RNA based therapeutics, peptides, drug combinations [77].

2.12 Role of Long Noncoding RNA

Long noncoding RNAs (lncRNAs) can often be transcripts of much more than 200 nucleotides whilst not having an obvious protein-coding function [78]. LncRNAs embrace diverse sorts of transcripts, inclusive of enhancer RNAs, small nucleolar RNA (snoRNA) hosts, intergenic transcripts, as well as transcripts which have antisense orientation [79]. The lncRNAs have most certainly been proven to be associated with dosage-compensation, epigenetic regulation, imprinting, cell cycle control, nuclear in addition to transcription, translation, splicing, cytoplasmic trafficking, cell differentiation [80]. lncRNAs can potentially work as scaffolds, guides, and certainly decoys and as a consequence have the possibility to control gene expression as well as spatial localization contained in the cell [79,81]. Escalating exploration facts signifies that abnormal act of expression of lncRNAs performs an indispensable function in carcinogenesis [81]. lncRNA offers the source and certainly justification to improve applications of lncRNA as disease markers and therapeutic targets and these lncRNAs have the ability to communicate with DNA, mRNA, ncRNAs as well as proteins to regulate cellular physiology, can be deregulated throughout diseases for instance cancer, and could establish the foundation for the therapeutic treatment [82]. Regardless of the fact that all natural and moreover combined concept that includes lncRNA along with various other proteins and genes will certainly be essential to develop safe and effective therapies. RNA genes may very well be of extreme benefit by facilitating unique opportunities for treatment [82].

2.13 Blockade of PD-1/PD-L1 Pathway

The tumour cells escape from the host immunity by a process called cancer immunoediting [83, 84]. PD-1(programmed cell death-1) receptor expresses on activated T cells interacts with its ligand PD-L1 expresses on various sorts of tumour cells facilitates tumours cells to escape

from the host immunity and prevents recruitment of new cytotoxic T-cells to the site of a tumour [84, 85]. According to preclinical studies antitumor activity and T-cell, the response can be enhanced by inhibiting the interaction between the PD-1 receptor and its ligand PD-L1 [86,87,88,89].

Therefore, to block this interaction inhibitor for PD-1 and PD-L1 have been designed and approved by FDA summarized in Table 3 [85] .

Table 3. Summarizes monoclonal antibodies approved by FDA [85]

Drug	Status	Target
Atezolizumab	FDA approved	PD-L1
Nivolumab	FDA approved	PD1
Pembrolizumab	FDA approved	PD1
MEDI4736	FDA approved	PD-L1

3. CONCLUDING REMARKS

Cancer therapy exploration is currently being escalated because of the fact that highly effective assistance is yet to be found. Traditional Cytotoxic agents which were used to deal with cancer could hardly discriminate amongst the cancerous tumour cells and healthy and balanced cells. The above-acknowledged therapies are recently progressed and some of them have shown potentially promising results in clinical studies namely Anti-Inhibitor of Apoptosis Drugs [90,91], Angiogenesis inhibitors [92,93] and Liposomal mediated drugs in the market as well as clinical stage reviewed in [94]. A few of the most promising solutions are described in this article and much more in the early development stage.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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