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35 Year Research History of Cytotoxicity and Cancer: a Quantitative and Qualitative Analysis

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RESEARCH ARTICLE

35-Year Research History of Cytotoxicity and Cancer: a Quantitative and Qualitative Analysis

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Abstract

Cancer is the leading cause of morbidity and mortality worldwide, characterized by irregular cell growth. Cytotoxicity or killing tumor cells that divide rapidly is the basic function of chemotherapeutic drugs. However, these agents can damage normal dividing cells, leading to adverse effects in the body. In view of great advances in cancer therapy, which are increasingly reported each year, we quantitatively and qualitatively evaluated the papers published between 1981 and December 2015, with a closer look at the highly cited papers (HCPs), for a better understanding of literature related to cytotoxicity in cancer therapy. Online documents in the Web of Science (WOS) database were analyzed based on the publication year, the number of times they were cited, research area, source, language, document type, countries, organization-enhanced and funding agencies. A total of 3,473 publications relevant to the target key words were found in the WOS database over 35 years and 86% of them (n=2,993) were published between 2000-2015. These papers had been cited 54,330 times without self-citation from 1981 to 2015. Of the 3,473 publications, 17 (3,557citations) were the most frequently cited ones between 2005 and 2015. The topmost HCP was about generating a comprehensive preclinical database (CCLE) with 825 (23.2%) citations. One third of the remaining HCPs had focused on drug discovery through improving conventional therapeutic agents such as metformin and ginseng. Another 33% of the HCPs concerned engineered nanoparticles (NPs) such as polyamidoamine (PAMAM) dendritic polymers, PTX/SPIO-loaded PLGAs and cell-derived NPs to increase drug effectiveness and decrease drug toxicity in cancer therapy. The remaining HCPs reported novel factors such as miR-205, Nrf2 and p27 suggesting their interference with development of cancer in targeted cancer therapy. In conclusion, analysis of 35-year publications and HCPs on cytotoxicity in cancer in the present report provides opportunities for a better understanding the extent of topics published and may help future research in this area.

Keywords: Cancer - anticancer treatments - cytotoxicity - highly cited papers - cancer therapy

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Introduction

Cancer is a common disease characterized by abnormal growth of the cells. It is one of the leading causes of morbidity and mortality worldwide and more than 589,430 people died from cancer in the United States in 2015. According to the World Health Organization (WHO), the numbers of new cancer cases is expected to rise by about 70% over the next 20 years (Siegel et al., 2015). Cancer develops in four steps initiating from turning the normal cells into tumors to their promotion and conversion to malignancy leading to the invasion at the progression stage (Cooper, 2000). There are more than 100 types of cancers of which lung, prostate, colon, rectum, stomach and liver are the most common sites of cancer among men and breast, colon, rectum, lung, cervix and stomach are the most common sites of cancer among women. Several causal factors, including genetic and environmental conditions play a critical role in the etiology and pathogenesis of cancer (Migliore and Coppedè, 2002; Sadikovic et al., 2008). Treatment of cancer via combination of surgery, radiation, and drugs, eradicates tumors or slows down their growth, depending on the type and stage of cancer. Many patients who receive treatment for cancer have a risk of developing long-term side effects. Early detection and efficient therapy of cancer may improve patient survival (Vanneman and Dranoff, 2012; DeSantis et al., 2014)

The therapeutic activity of most anticancer drugs used in chemotherapy is based on their general toxicity

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to living cancer cells. Cytotoxic drugs circulate in the body to destroy cancer cells by interfering with their ability to proliferate and grow. Due to the side effects of the cytotoxicity-based drugs in cancer therapy, novel strategies have been designed to provide less toxic treatment and adverse effects (Corrie, 2008; Wang et al., 2013; Pankova et al., 2014). Novel advances in the drug discovery and development have opened new insights into disrupting tumor-specific cell signaling, cell division, energy metabolism, gene expression, drug resistance and blood supply by modern antitumor targeted models (Nagle et al., 2004). Given the rapid development of preclinical and clinical studies of cytotoxicity-based pharmaceutical products, this study was conducted to analyze the quality and quantity of the researches performed with relevance to the role of cytotoxic drugs in cancer therapy from 1981 to December 2015. Results of this study can provide an insight on the evolving research interest in this field.

Materials and Methods

The documents evaluated in this study were sourced from Web of Science (WOS) Core Collection from Thomson Reuters Web of Science (formerly ISI Web of Knowledge), Philadelphia, PA, USA. The online cytotoxicity and cancer data from 1981 to December 2015 were quantitatively and qualitatively analyzed.

Quantitative data analysis

To analyze the cytotoxicity and cancer data quantitatively, the Web of Science Core Collection were sequentially and systematically searched from 1981 to December 2015 for the key words "cytotoxicity and cancer" OR "anticancer and cancer". Documents with the above key words in the "Title" were selected for data analysis. Identified parameters for data analysis included the publication year, the number of times they were cited, research area, source, language, document type, countries, organization-enhanced and funding agencies.

Qualitative data analysis

For qualitative analysis, the historical method was applied. This method was utilized to review and investigate the initiation and development of cytotoxicity and cancer as documented in publications in WOS from 1981 to December 2015 and to explore cytotoxicity and

Table 1. Distribution of Publications by Research Area and Source Title

Research area	N (% of 3473)	Source title	N (% of 3473)
Oncology	1,452 (41.9)	Anticancer Research	108(3.1)
Pharmacology and pharmacy	794 (22.9)	Cancer Research	107(3.1)
Biochemistry molecular biology	406 (11.7)	Clinical Cancer Research	74(2.1)
Chemistry	342 (9.9)	European Journal of Cancer	64(1.8)
Research experimental medicine	199 (5.7)	Journal of Clinical Oncology	60(1.7)
Cell Biology	189 (5.5)	Plos One	55(1.6)
Science technology other topics	161 (4.6)	Cancer Letters	53(1.5)
Biotechnology applied microbiology	106 (3.1)	International Journal of Oncology	52(1.5)
Toxicology	100 (2.9)	Oncology Reports	49(1.4)
Materials science	88 (2.5)	Molecular Cancer Therapeutics	49(1.4)
Urology nephrology	85 (2.5)	Annals of Oncology	49(1.4)
Endocrinology metabolism	83 (2.4)	British Journal of Cancer	47(1.4)
Biophysics	76 (2.2)	Biochemical Pharmacology	43(1.2)
Immunology	67 (1.9)	Anti Cancer Drugs	43(1.2)
Plant sciences	66 (1.9)	International Journal of Cancer	(39)1.1
Gastroenterology hepatology	60 (1.7)	Cancer Chemotherapy and Pharmacology	39(1.1)
Genetics heredity	58 (1.7)	Faseb Journal	39(1.1)
Integrative complementary medicine	57 (1.6)	Journal of Urology	36(1.0)
Life sciences biomedicine other topics	55 (1.6)	Breast Cancer Research and Treatment	31(0.9)
Food science technology	50 (1.4)	Biochemical and Biophysical Research Communications	31(0.9)

Table 2. Distribution of Publications by Country, Organization-Enhanced and Funding Agency

Country	N	Organizations-enhanced	N	Funding agency	N
USA	1054	NIH	102	National Natural Science Foundation of China	125
China	431	NIH NCI	89	NIH	90
Japan	427	Unicancer	51	NCI	22
South Korea	212	Utmd Anderson Cancer Center	49	Ministry of Education Science and Technology	20
India	169	University of California System	47	Ministry of Education Culture Sports Science and Technology of Japan	18
Italy	160	Institut National De La Sante Et De La Recherche Medicale Inserm	45	Fundamental Research Funds For the Central Universities	18
Germany	152	Seoul National University	44	National Science Council Taiwan	17
France	139	National Taiwan University	42	National Science Council of Taiwan	12
Taiwan	131	University of Iowa	36	National Science Council of The Republic of China	11
England	122	Centre National De La Recherche Scientifique Cnrs	32	NRF	11

NIH, National Institutes of Health; NCI, National Cancer Institute; NRF, National Research Foundation of Korea

Table 3. Characteristics of the 17 Highly Cited Publications

Author	Country	Institute	Document	Journal	IF	Cited	Paper concept
Barretina (2012)	USA	Broad Inst Harvard & MIT	Original	Nature	41.45	825	The cancer cell line encyclopedia (CCLE) database contains a large, annotated cell-line collection of gene expression, chromosomal copy number and sequencing data from 947 human cancer cell lines, together with pharmacological profiles for 24 anticancer drugs across 479 of the cell lines. CCLE can be applied for detection of genetic, lineage, and gene-expression-based predictors of drug sensitivity, which can speed up the emergence of 'personalized' therapeutic regimens.
Deeb et al. (2007)	USA	Roswell Pk Canc Inst	Review	Nat. Rev. Cancer	37.4	526	Calcitriol, a vitamin D analogue, acts as a potential anticancer agent. This drug has anti-proliferative effects which activates apoptotic pathways and inhibits angiogenesis as well as potentiates the anticancer effects of many anticancer agents. This drug can be applied for prevention and treatment of cancer.
Kukowska-Latallo (2005)	USA	University of Michigan	Original	Cancer Res.	9.32	503	polyamidoamine (PAMAM) dendritic polymer nanocarriers targeting methotrexate anticancer drug improves antitumor activity in the immune-deficient mice bearing human KB tumors. This conjugate possesses less toxicity and higher therapeutic responses which is not obtained with a free methotrexate.
Chu (2008)	USA	University of Miami	Review	Nat. Rev. Cancer	37.4	426	The p27, a Cdk inhibitor, regulates cell proliferation, cell motility and apoptosis. The role of p27 in the cellular pathways has been identified by various post-translational modifications. Since alteration of synthesis and degradation of p27 is involved in developing cancer, testing the p27 levels is suggested for prognosis and treatment of cancer.
Kurai (2007)	Japan	University of Tottori	Original	Clin. Cancer Res.	8.72	199	Cetuximab is a chimeric mouse-human antibody which has potential antibody-dependent cellular cytotoxicity (ADCC) activity against epidermal growth factor receptor (EGFR)-expressing lung cancer cell lines. The ADCC of cetuximab provides a possible antitumor mechanism for combination therapy in patients with lung cancer.
Airley (2007)	England	University of Nottingham	Review	Chemotherapy	1.28	166	Alterations in the cellular aerobic respiration characteristics such as hypoxia, glucose transport and metabolism and lactate production are the most important epigenetic and bioenergetic adaptations in cancer. These features can be applied as novel targets for anticancer therapy.
Foldbjerg (2011)	Denmark	University of Aarhus	Original	Arch. Toxicol.	5.98	166	Evaluation of silver nanoparticles (Ag NPs) cytotoxicity in the human lung cancer cell line (A549) shows that Ag NPs can increase ROS production leading to apoptosis and necrosis of the cells.
Homma (2009)	Japan	University of Tsukuba	Original	Clin. Cancer Res.	8.72	151	NF-E2-related factor 2 (Nrf2) is an important transcription regulator for antioxidant enzymes for detoxification expressed in the cancer cells. Since Nrf2 is critical for both proliferation of cancer cell and their resistance to drugs, it is suggested as a potential target for enhancing the efficacy of anticancer drugs
Lopez-Lazaro (2008)	Spain	University of Seville	Review	Mol. Nutr. Food Res.	4.6	129	Curcumin as a main active component of spice turmeric has pro-oxidant and antioxidant properties. It is known as anticancer and carcinogenic compound which induces apoptosis and inhibits tumor formation in animal models. Therefore, this derivative can be used as a pharmacologically safe agent in cancer therapy.
Heiser (2012)	USA	Lawrence Berkeley National Laboratory	Original	P. Natl. Acad. Sci. USA	9.67	108	Testing of 77 therapeutic compounds showed that breast cancer cell lines shoed various subtype-, pathway-, and/or genomic aberration-specific responses to approximately one third of the compound. Devloping of molecular assay tests for the involved mechanisms in response to these compounds can be informative for prediction of clinical response.
Rattan (2011)	USA	Mayo Clinic	Original	Neoplasia	4.92	94	Metformin inhibits proliferation, angiogenesis and metastatic of the ovarian cancer cells suggesting that this drug can be used in treatment of ovarian cancer treatment.
Deng (2013)	USA	MIT	Original	Acs. Nano.	14.41	80	The layer-by-layer nanoparticles for codelivery of small interfering RNA (siRNA) and doxorubicin as an anticancer drug significantly reduces triple-negative breast cancer cells. This composite is supposed to be used fr aggressive and resistant cancer treatment.

Table 3. (Continued) Characteristics of the 17 Highly Cited Publications

Dong (2013)	China	Changchun Inst Appl Chem	Original	Adv. Mater.	17.49	67	The developed novel 980 nm laser-driven hydrophobic anticancer drug delivery platform based on the CuS nanoparticles is an efficient synergistic therapy in cancer cells in vivo which opens up new opportunities for its biological and medical applications.
Schleich (2013)	Belgium	Catholic University of Louvain	Original	Int. J. Pharmaceut.	3.65	44	Development of multifunctional paclitaxel (PTX)/ superparamagnetic iron oxide (SPIO)-loaded poly lactic-co-glycolic acid (PLGA)-based nanoparticles for mouse colon cancer therapy and magnetic resonance imaging suggest future usability of nanomedicine for simultaneous molecular imaging, drug delivery and real-time monitoring of therapeutic response.
Fang (2014)	USA	University of California	Original	Nano. Lett.	13.59	33	The cell-derived nanoparticles can mimic many natural properties of the original cells. The membrane of these cancer cells coated by nanoparticles is an effective method for introducing multiple membrane antigens and surface functionalities to different anticancer drugs or vaccines and drug delivery.
Park (2014)	South Korea	Korea Inst Sci & Technol	Original	J. Ginseng. Res.	2.81	22	The ginsenosides is the main active component of ginseng. The heat-processed method for American ginseng for isolation of ginsenoside Rg3 epimers has improved the antitumor activity of this derivative on gastric cancer cells through inducing the caspase-3, caspase-8, and caspase-9 activity leading to the death of apoptosis in cancer cells.
Pennati (2014)	Italy	Fdn IRCCS Ist Nazl Tumori	Original	Biochem. Pharmacol.	5	18	The epithelial-to-mesenchymal transition plays a key role in resistance to chemotherapy in human cancer cells. Replacement of miR-205 in castration-resistant mesenchymal prostate cancer cells impairs autophagy and improves the cisplatin cytotoxicity.

cancer trend. Based on this review, we may be able to forecast possible future development in cancer therapy.

Results and Discussion

Quantitative data analysis of the total publications

Number of publications and their citations over the 35 years. Following search of ISI WOS, a total of 3,473 publications on cytotoxicity and cancer were published between 1981 and December 2015. These publications have been cited 54,330 times between 1983-2015 and 1,079 were self-cited. Distribution of the publication and citation ratio over a period of 35 years is shown in Figure 1. Generally, an increase of the trend of both publication and citation ratio is seen during 35 years as shown in figure 1 revealing the importance of this topic. The number of publications has grown from 3 in 1981 to 419 in 2014 (about 140 times) and approximately 86% (N=2,933) of publications have been published between 2000 and 2015. Together these results show that this subject is still relevant and significant topic among researchers.

Distribution of publications by research area and source titles

In the WOS, 3,473 publications were categorized into 78 research areas. Overall, more than 84% of WOS research areas of published papers are more related to four fields, oncology, pharmacology pharmacy, biochemistry molecular biology, and chemistry. In addition 3,473 publications were published in 857 academic journals between 1981 and 2015. The percentage of the papers published in the top journals and research area are shown in Table 1.

Distribution of publications by document type and language

Figure 2 shows that of 3,473 publications, 2,564 (74%) of them were original articles followed by 651 (19%) meeting abstracts, 139 (4%) review papers, 70 (2%) proceedings paper, 40 (1%) editorial material and the remaining 62 (2%) compose of other document types such as letter, note, news item, book chapter. Approximately, 3,158 (91%) of these papers were published in non-open access journals. The language of 3,452 (99.4%) publications was English and the remaining papers were published in other languages, including French, German, Russian, Japanese, Polish and Portuguese.

Distribution of publications by country, organization-enhanced and funding agency

The 10 top countries, institutions and funding agencies involved in the publications have been listed in the Table 2. The 3,473 publications were contributed by 87 countries. USA with the highest number (30.4%) together with China (12.4%), Japan (12.3%), South Korea (6.1 %), India (4.9 %), Italy (4.6 %), Germany (4.4 %), France (4%), Taiwan (3.7 %) and England (3.5 %) were the top ten countries publishing articles related to the cytotoxicity and cancer. National Institutes of Health (NIH) USA (3%), NIH National Cancer Institute (NCI) (2.5 %) and Unicancer (1.5%) were the top three institutions producing the largest number of publications. The 3,473 publications were funded by 2,244 agencies in the world. The National Natural Science Foundation of China (3.6%), National Institutes of Health (2.6%) and National Cancer Institute (0.7%) were the top three foundations supporting cytotoxicity and cancer research.

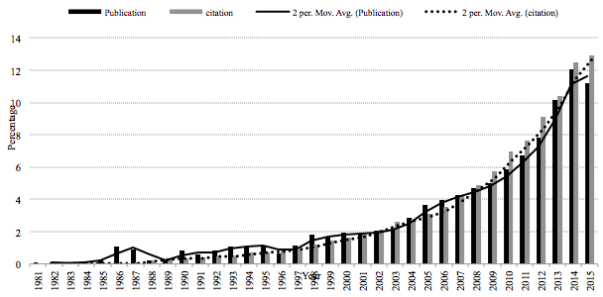

Figure 1. Distribution of 3,473 Publications (Black Boxes) and their 54,264 Citation (Gray Boxes) Ratios and the Related Trends Over a 35-Year Period

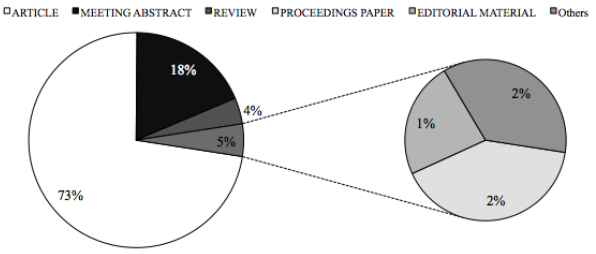

Figure 2. Publication Types in the ISI Web of Knowledge

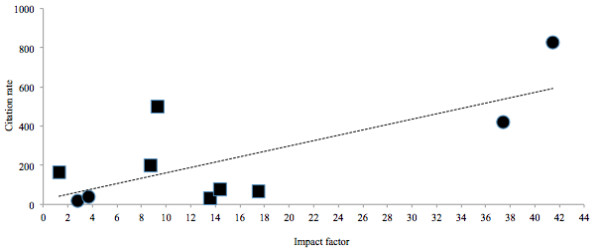

Figure 3. Analysis of Relationship between Journal Impact Factors and Number of Citations. Amongst 10 papers (circles and black boxes) with highest effect on the correlation,four papers (circles) increased the r and decreased P values.

Quantitative and qualitative data analysis of the 17 highly cited publications

Quantitative data analysis: Of 3,473 publications, 17 papers published between 2005 and 2015 as the most frequently cited articles are presented in table 3. The sum of the times cited without self-citations was 3,584 with h-index of 17. Of 17 publications, 59% (10) were published between 2011 and 2014. All highly cited papers (HCPs) were published in English and among them, 76.5% (13) of publications were original articles and 23.5% (4) were reviews. Approximately, 53%, 41% and 23.5% of the publications were generated by academic and research centers in USA, Europe (England, Denmark, Belgium, Spain, Italy) and Asia (Japan, South Korea and Peoples Republic of China), respectively. According to the WOS categories for these highly cited papers, about 41% of them are in Oncology fallowed by 17.64% for each of Pharmacology Pharmacy, Nanoscience Nanotechnology, Materials Science Multidisciplinary, Chemistry Physical And Chemistry Multidisciplinary Categories, 11.7% for Physics Condensed Matter, Physics Applied, Multidisciplinary Sciences and 6% For each Of Toxicology, Plant Sciences, Integrative Complementary Medicine, Food Science Technology as well as Chemistry Medicinal category. In addition, the top two most cited articles (825 and 526) (Deeb et al., 2007; Barretina et al., 2012) were published in the Nature and Nature Reviews Cancer with impact factor of 41.45 and 37.40, respectively. Analysis of relationship between journal impact factors and citation rates of HCPs showed a strong correlation between these variables ($r = 0.784$, $p = 0.0002$) as demonstrated in Figure 3. Amongst the seventeen HCPs, 10 papers had the highest effect on this correlation and among them, four papers (circle), particularly the paper published in Nature (impact factor 41.25, citation 825) related to the comprehensive online CCLE database(Barretina et al., 2012), increased the r and decreased p values (Deeb et al., 2007; Barretina et al., 2012; Schleich et al., 2013; Park et al., 2014).

Qualitative data analysis: Discovery and development of anticancer drug against human cancer as the second leading cause of death worldwide are the key focus of the pharmaceutical industry and research organizations. Generating a comprehensive preclinical database is crucial for designing clinical development programs. Amongst the HCPs, the study with the highest number of citations (about 24% of 3,557) has provided a public access to the "cancer cell Line encyclopedia (CCLE)" database (http://www.broadinstitute.org/ccle)(Barretina et al., 2012). The CCLE database is a large-scale genomic database of 947 human cancer cell lines of 36 tumour types. The pharmacological profile of 24 anticancer drugs has been coupled with 479 cell lines offering detection of genetic, lineage, and gene-expression-based predictors of drug sensitivity. These large, annotated cell-line collections are applicable for genetic predictions of drug response in the preclinical setting and their incorporation into cancer clinical trial design could speed the emergence of 'personalized' therapeutic regimens. The remaining 16 HCPs, they have been categorized into three following groups on the basis of their main concept.

Anticancer agents in cancer therapy

Approximately, 29% (five original papers with about 25% of 3,557 citations) of the 17 HCPs have investigated cytotoxic properties of various compounds for development of anticancer therapeutics (Table 3). In this group, three original papers have focused on the discovery or development of anticancer agents including 77 therapeutic compounds, metformin and ginseng (Rattan et al., 2011; Heiser et al., 2012; Park et al., 2014). Evaluation of anticancer properties of the 77compounds studied (12% of 879 citations) on breast cancer cell lines showed various subtype-, pathway-, and/or genomic aberration-specific responses to approximately one third of the compound (Heiser et al., 2012). Development of molecular assay tests for the mechanisms involved in response to these compounds is informative for prediction of clinical response. The second paper (11% of 879 citations) (Rattan et al., 2011) which concerned the evaluation of the metformin on ovarian cancer cell line revealed a high

efficacy of this drug alone or in combination with cisplatin in inhibiting tumor cell proliferation, angiogenesis and metastatic spread. In another report (2% of 879 citations) (Park et al., 2014), researchers could successfully improve the pharmaceutical effect of American ginseng on human gastric cancer through a heat-processing method. The last two papers reviewed the pooled evidence on calcitriol (60% of 879 citations) and curcumin (15% of 879 citations) as potential anticancer agents(Deeb et al., 2007; Lopez, 2008). Calcitriol is a vitamin D analogue possessing anti-proliferative, apoptotic activating and angiogenesis inhibition effects which have potential in prevention and treatment of cancer(Deeb et al., 2007). Curcumin, the main active component of spice turmeric, has the prooxidant and antioxidant properties. This anticancer compound induces apoptosis and inhibits tumor formation in animal models. Hence, this derivative can be used as a pharmacologically safe agent in cancer therapy (Lopez, 2008).

Nanoparticle technology in cancer therapy

More than one third (six original papers with 25% of 3557 citations) of 17 HCPs have focused on development and application of engineered nanoparticles (NPs) in management of cancer. The NPs are unique biomedical research tools in targeted drug delivery which enable reduction of adverse effects associated with conventional chemotherapy. The NPs in this category include polyamidoamine (PAMAM) dendritic polymer nanocarriers (Kukowska-Latallo et al., 2005), silver nanoparticles (Ag NPs) (Foldbjerg et al., 2011), layer-by-layer nanoparticles (LBL-NPs) (Deng et al., 2013), 980 nm laser-driven hydrophobic platform based on the CuS nanoparticles (Dong et al., 2013), paclitaxel (PTX)/ superparamagnetic iron oxide (SPIO)-loaded PLGA-based NPs (Schleich et al., 2013) and cell-derived NPs (Fang et al., 2014). Among the papers in this category, the modified PAMAM dendritic polymers of less than 5nm in diameter have been predominantly cited (57% of 893 citations). Conjugation of this nanocarrier with methotrexate (an anticancer drug) can improve antitumor activity with higher therapeutic efficacy and lower toxicity than free methotrexate (Kukowska et al., 2005). The study by Foldbjerg (32% of 893 citations) evaluated the uptake and cytotoxic effects of well-characterized Ag-NPs on human lung cancer cell line suggested that these particles could induce oxidative stress and result in cell apoptosis (Foldbjerg et al., 2011). Further paper (9% of 893 citations) developed modular and controlled LBL-NPs platform for codelivery of small interfering RNA (siRNA) and doxorubicin (an anticancer drug) for aggressive and resistant cancer treatment for triple-negative breast cancer cells (Deng et al., 2013).Another interesting report (8% of 893 citations) (Dong et al., 2013) was related to a novel 980 nm laser-driven hydrophobic anticancer drug delivery platform based on the CuS NPs. This vehicle was constructed for efficient synergistic therapy of cancer cells and opens up new opportunities for biological and medical applications. Subsequent study (5% of 893 citations) (Schleich et al., 2013) on co-encapsulated PTX/SPIO-loaded PLGA-based NPs in colon cancer demonstrated that these NPs inhibited growth and development of cancer cells. This study has enabled simultaneous targeting imaging, drug delivery and real-time monitoring of therapeutic response. The last publication in this group (4% of 893 citations) (Fang et al., 2014) on cell-derived NPs revealed that coating polymeric NPs with cancer cell membrane was an effective method for introducing multiple membrane antigens and surface functionalities for cancer immunotherapy and anticancer drug delivery.

Potential targets in cancer therapy

Nearly, one third (five papers with 29% of 3515 citations) of 17 HCPs investigated the cyclin-dependent kinase (Cdk) inhibitor p27 (Chu et al., 2008), cetuximab (a chimeric antibody) (Kurai et al., 2007), glucose transport and metabolism (Airley and Mobasheri, 2007), NF-E2-related factor 2(Nrf2) (Homma et al., 2009) and miR-205 (Pennati et al., 2014) as potential targets for anticancer drugs. Out of 960 citations in this group, 426 (44.5%) concerned to p27. This review paper comprehensively investigated the role of the tumor suppressor p27 in cancer. P27 regulates transition of the G0 to S phase, thereby alters cell proliferation and cell motility and apoptosis. Since p27 is inactivated in cancer through impaired synthesis, accelerated degradation and by mislocalization, the levels of this protein can be used to monitor and treatment of cancer and prevention (Chu et al., 2008).

The next HCP (21% of 960 citations) (Kurai et al., 2007) in this category studied the antibody-dependent cellular cytotoxicity mechanisms induced by cetuximab, an EGFR inhibitor used for treatment of various types of cancers. Epidermal growth factor receptor (EGFR) as an oncogene involves in the development of cancer. The majority of human malignant cells highly express glucose transporters (GLUT) family members which may be targeted by anticancer drugs. The properties and roles of GLUT family in development of cancer have been extensively discussed by the authors of next HCP (17% of 960 citations) (Airley and Mobasheri, 2007). The important role of GLUT proteins in the hypoxic regulation of glucose transport, anaerobic metabolism and angiogenesis in cancer suggests their potential as novel targets in cancer therapy (Airley and Mobasheri, 2007).

Further study (16% of 960 citations) (Homma et al., 2009) examined the role of the Nrf2, a leucine zipper protein that regulates transcription of antioxidant proteins. These molecules protect cells against oxidative damage triggered by injury and inflammation. This study reported that functional inhibition of Nrf2 in the lung cancer cell lines suppresses both proliferation and resistance to anticancer drugs suggesting Nrf2 is a potential target for enhancing efficacy of the anticancer drugs (Homma et al., 2009).

The last publication in this category (2% of 960 citations) (Pennati et al., 2014) targeted microRNA-205 (miR-205) that regulates epithelial to mesenchymal transition and tumor invasion and chemo-resistant phenotype in chemotherapy. Replacement of miR-205 in castration-resistant mesenchymal prostate cancer cells impaired autophagy and improved the cisplatin cytotoxicity (Pennati et al., 2014).

In conclusion, In conclusion, as cancer and its treatment have always been a major public health concern, the quantitative evaluation of overall publications together with qualitative analysis of HCPs presented in this study are informative and supportive for drug discovery and development in cancer therapy.

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