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Review

Percutaneous penetration of anticancer agents: Past, present and future

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ABSTRACT

Cancer occurs as a result of alterations in oncogenes, tumor-suppressor genes, and microRNA genes. Over the past few decades, efforts have been made to understand the dominant oncogenes and tumor suppressor genes whose respective activation/upregulation or loss of function serve to impart aberrant properties on normal cells. Cancer continues to be a source of public health concern due to widespread prevalence, morbidity and mortality. The most common types include but are not limited to lung, prostate, colorectal, breast, ovarian and skin cancers. In 2012, there were more than 8 million deaths worldwide related to cancer from 14 million new cases. Cancer chemotherapy frequently requires long periods of multiple intravenous infusions which may compel patients to abandon treatment. One approach to overcome this challenge is through the use of transdermal drug delivery systems. The major obstacle with transdermal drug delivery is that the stratum corneum, which is the outermost layer of the skin, hinders the penetration of therapeutic agents. An avalanche of techniques is available to enhance the penetration of anticancer agents across the skin including iontophoresis, sonophoresis, microneedles, prodrugs, microemulsions and elastic liposomes. In this review, attention is focused on the numerous techniques used to overcome the skin barrier and enhance the percutaneous penetration of anticancer agents.

Contents

1. Introduction

In 2012, there were more than 8 million deaths worldwide related to cancer from 14 million new cases [1] Despite intensive research, cancer is one of the main causes of death globally with considerable economic and social burden [21]. It has been

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postulated that cancer is caused by changes in oncogenes, tumor-suppressor genes, and microRNA genes [2]. These alterations are usually somatic events, although germ-line mutations can lead to familial cancer [2]. Cancer is a fully developed (malignant) tumor capable of invading and destroying the underlying mesenchyme [3]. It is well documented that cancer has the following distinct capabilities- the ability to resist cell death, sustain proliferative signaling, evade growth suppressors, induce angiogenesis, enable replicative immortality, and activate invasion and metastasis [4]. Reprogramming of energy metabolism and evasion of immune destruction have also been added as emerging hallmarks [4]. One postulate is that malignant tumors evolve along multistage programs that require establishment of a tumor stroma, neo-angiogenesis, and reprogramming of cell metabolism, leading to the expression of tumor associated antigens [5].

Over the past few decades, efforts have been made by researchers to understand the dominant oncogenes and tumor suppressor genes whose respective activation/upregulation or loss of function serve to impart aberrant properties on normal cells, thus contributing to their transformation into the cancerous cells that form the basis for malignancy [6]. For instance, Sibbesen et al. showed that malignant T cells display down-regulation of miR-22 expression and provided mechanistic evidence that Jak3/STAT signaling inhibits the expression of this gene [7]. The authors postulated that this chain of events results in elevated expression of MYCBP and MAX (co-activators of the c-Myc oncogene), and NCoA1, a transcriptional regulator [7].

Sometimes it may not be possible to identify one unifying genetic event or one particular oncogene central to malignant transformation and cancer progression [7]. For instance, deregulation of signaling pathways including Signal Transducers and Activators of Transcription (STAT), src kinases, c-Myc, COX-2, NFκB, GATA3, TOX, and embryonic stem cell regulators seem to play an important role in the pathogenesis of cutaneous T-cell lymphomas (CTCLs) [6]. CTCLs are a diverse group of non-Hodgkin lymphomas derived from T cells that traffic to the skin. There are different clinical subtypes of CTCL including mycosis fungoides (MF) and leukemic CTCL [8].

There is also increasing evidence that the expression of microRNA (miRNA), the main post-transcriptional regulation mechanism, changes in cancer cells [9]. Cancer cells differ from normal cells in that they no longer respond to normal growth-controlling mechanisms [3]. According to Radić et al., a further complication is that some cancer cells may not grow at all while others respond only to certain regulatory mechanisms [3]. Carcinogenesis is a multistage process with series of changes after the initiation step has been induced by a carcinogen, oncovirus [10] or other factors. Initiation, which is the primary and essential step in the process occurs at a fast pace but once the initial change has taken place, the cells may persist for some time, perhaps the life span of the person [3].

Several mechanisms by which environmental carcinogens induce cancers have been suggested. There are carcinogens that damage DNA directly (genotoxic agents) and those that act by different mechanisms (non-genotoxic agents). Genotoxic agents are most frequently electrophiles which cause mutations affecting oncogenes or tumor-suppressor genes. Non-genotoxic carcinogenic agents may disrupt normal cell cycle and apoptotic regulation, induce oxidative stress, disrupt the immune system, activate CYP450 enzymes, and disrupt normal metabolism [11].

It has been suggested that the most likely site for the primary event leading to cancer is in the genetic material (DNA), although there are other possibilities. Carcinogens are thought to damage or destroy specific genes probably in the stem cell population of the affected tissue [3]. During the past 38 years, it has also become evident that numerous viruses play important roles in the development of human neoplasms; about 15% to 20% of cancers are linked to viral infections [12]. Viruses that are associated with human malignancies include human T-lymphotropic virus type 1, human papillomavirus, human herpesvirus 4, hepatitis B virus and hepatitis C virus [12]. It is also apparent that the BK virus (a member of the polyomavirus family) could have a potential role in the development of bladder cancer [10]. Indeed, it was observed that the prevalence and titer of antibodies to BK virus (BKV) was higher in bladder cancer patients and there was also a higher percentage of BKV genome present in those suffering from bladder cancer in comparison with cancer free patients[10].

The most common types of malignant tumors include but are not limited to lung, prostate, colorectal, breast, ovarian, skin cancers and leukemia. Less common but equally deadly is the squamous cell carcinoma of the oropharynx [13]. Lung cancer is the top killer cancer in both men and women in the United States of America (USA) [14]. Colorectal cancer is one of the most common cancers with the prevalence estimated at 945,000 cases globally in 2000 and mortality approximately 492,000 persons [15]. Prostate cancer (PC) is the most common male malignancy in developed countries and its mortality only lags behind lung and colorectal cancer [16].

About 15% of women are diagnosed with breast cancer in the reproductive age and it is the leading cause of cancer death in women between 35 and 55 years of age [17]. Most breast cancers occur sporadically due to chronic exposure to multiple environmental carcinogens; this multistep process results in the transformation of breast cells from noncancerous to precancerous and then to cancerous [18]. Ovarian cancer is the second most common gynecological tumor in advanced countries and the most lethal. In the United States, there are about 22,000 new cases of ovarian cancer annually [19]. It has been documented that in the USA, approximately 1 in 5 people will develop skin cancers [20]. These disorders account for nearly 15 thousand deaths and more than three billion dollars annually in medical costs [20].

It is documented that skin cancer is the most common form of malignancy, although it is not the deadliest [21]. The most common forms of skin cancer are basal cell carcinoma ~2.8 million U.S. cases every year, and squamous cell carcinoma (approximately 700,000 U.S. cases annually)[21]. Even though malignant melanoma represents only a very small proportion of skin cancers ~74,000 U.S. cases annually, it accounts for most skin cancer deaths [21].

Skin cancers are categorized according to the cell from which they arise. The three most common types of skin cancer are basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs) and malignant melanomas [20] In 2010, an estimated 68,130 new cases of melanoma were diagnosed in the USA and approximately 8700 patients died of the disease[20]. Melanoma is a malignant skin cancer with a global incidence of 232,000 new cases in 2012 [22]. There were 55,000 deaths from melanoma reported in the same year [22]. The signal transducer and activator of transcription 3 (STAT3) has been shown to be involved in the survival, proliferation, angiogenesis, metastasis and immune evasion of cancer cells [22]. More than 3.5 million cases of non-melanoma skin cancer are reported annually in the United States of America. Approximately 137,310 new cases were projected for 2015 [23].

The human herpesvirus-8 (HHV-8) and immunosuppression have been known to cause Kaposi sarcoma (KS) [24,25]. KS is an intermediate, non-metastasizing vascular neoplasm which affects mainly the viscera, mucosa and the skin even though it has also been known to spread to lymph nodes and internal organs [24,26–28]. The disease usually presents as cutaneous lesions with or without involvement of internal visceral organs and/or lymph nodes [28]. Four epidemiological forms of KS have been identified: classic, African AIDS associated and iatrogenic [24]. The iatrogenic