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Review

Matrix metalloproteinase enzymes and their naturally derived inhibitors: Novel targets in photocarcinoma therapy

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ABSTRACT

The continuous exposure of skin to ultraviolet radiations generates reactive oxygen species leading to photoaging in which degradation of dermal collagen and degeneration of elastic fibers occurs. Matrix metalloproteinase [MMP] enzymes are the proteolytic enzymes which have significant potentiality of cleaving extracellular matrix [ECM] against Ultraviolet [UV] radiation. The important MMPs are MMP1, MMP2 and MMP7 which promote skin cancer when irradiated by UV rays. In lieu of this, the investigation of MMPs and their inhibitors are constantly being studied for successive results. Recent researches have focused on some traditionally used bioactive moieties as natural matrix metalloproteinases inhibitors (MMPIs) and emphasized on the need of more extensive and specific studies on MMPIs, so that a good combination of natural or synthetic MMPIs with the conventional drugs can be evolved for cancer chemotherapy. In this review, we discuss the current view on the feasibility of MMPs as targets for therapeutic intervention in cancer. This review also summarizes the role of small molecular weight natural MMPIs and a clinical update of those natural MMPIs that are under clinical trial stage.

Contents

Abbreviations: MMP, matrix metalloproteinase; MMPIs, matrix metalloproteinase inhibitors; ECM, extracellular matrix; SC, stratum coreneum; UVB, ultraviolet radiations B; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; DNA, deoxyribonucleic acid; CPD, cyclobutane pyrimidine dimmers; NER, nucleotide excision repair; TCR, transcription-coupled repair; GGR, global genome repair; LE, lupus erythematosus; XP, xeroderma pigmentosum; TTD, trichothiodystrophy; ODC, ornithine decarboxylase; MAPKs, mitogen activated protein kinase; NOS, nitric oxide synthase; TRAP, telomeric repeat amplification protocol; CBD, collagen binding domain; ACD, allergic contact dermatosis; AD, atopic dermatosis; SRF, skin respiratory factors; TRF, tissue respiratory factors.

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1. Introduction

Matrix metalloproteinase are the enzymes which have been vigorously studied for identifying their functions and role in the progress of cancer. They are the initiators of angiogenesis, metastasis, inflammation and other pathological consequences manifested in carcinoma. The idea of targeting MMPs as a therapeutic receptor in cancer treatment was laid down 30 years ago by Liotta et al. (Konstantinopoulos et al., 2008), by that time to now tremendous efforts have been made to target different MMPs for slowing the growth of cancer cells. Several clinical studies (Fisher et al., 2009) have demonstrated the promising aspects of MMPIs expression but very limited outcomes have been received. The utilization of Natural bioactives as a therapeutic drug targeting system toward MMPs in proliferation of photocarcinoma will be an innovative to support the traditional drug regimen for cancer (Mannello, 2006).

The human skin constitutes the most vital aspect in the defense mechanism against the exposure of ultraviolet radiation. It acts as an efficient barrier system to protect the underlying tissues from the external environment. But the intensity of incident solar radiation causes changes in the nature of skin. These changes can be fundamental, in order to protect the cells from the deleterious effect of ultraviolet radiations or it may be a pathological change rendering the provocation of biochemical alterations leading to the destruction of tissues (Soehnge et al., 1997). The alterations exhibited by the skin leads to inflammation, erythema, premature aging, fine lines and wrinkle formation, chapping and cracking and can develop into a severe pathological manifestation of atopic dermatoses, solar kerotosis, etc. (Gonzaga, 2009).

There are several mediators which through a predefined or an unknown mechanism can contribute in the controlling of the aging process. These mediators are either of herbal origin (Afaq, 2011; Saraf and Kaur, 2010) or the synthetic one. Depending upon the severity of photo-aging, the choice of adopting phytoconstituents as a remedy serves to be a safer option (Yaar and Gilchre, 2007). The characteristic of intrinsic aging is manifested by the atrophy of the dermis and epidermis and the flattening of dermal-epidermal junction. While the complications related to photo aging is dysplasia of epidermal cells, melanocytes heterogeneity and elastosis of the epidermis also termed as solar elastosis. The figure depicts the effect of ultraviolet radiations, generation of reactive oxygen species and cellular alterations causing photoaging and photocarcinogenesis (Fig. 1).

The herbal mediators chiefly the phytoconstituents are capable of treating the photoaging process at all levels which left untreated can lead to photocarcinogenesis (Afaq, 2011; Chanchal and Saraf, 2008):

- Gene longevity.
- Free radical scavenging.
- Reduction in cellular atrophy mediated by telomere shortening.

1.1. Impact of UV radiations

In skin cancer the normal restoring physiology of the epidermal and dermal cells against cell's excessive proliferation is completely paralyzed leading to the alteration in the normal cell signaling mechanism (Young, 2009). These changes are so specific that they give rise to new cellular characteristics like the production of new enzymes or complete alteration of enzymatic activities causing a dramatic mutational drift on the molecular cellular level. These shifts in biochemical pathways are very spontaneous in action and travel in traits to the upcoming progenies, leading to a complete mutation (Evans et al., 2004). On long term exposure to ultraviolet radiation, the protein encoding genes regulating cell division become mutated. These are the genes which participate and responsible for DNA repair, e.g. p53 genes (Evans et al., 2004). The hindrance of such genes from their normal biochemical functions leads to mutations in the cells. It has been estimated that approximately 35,000 genes in the human genome are associated with cancer and the number of genes associated with skin carcinoma is too less to be counted. Any change in their normal functioning can lead to a carcinoma. These malfunctioning genes can be broadly classified into three groups. The first is called proto-oncogenes which produce protein responsible for cell division or inhibiting normal cell death. Their mutated forms are termed as oncogenes (Thurstan et al., 2012). The second one, is known as tumor suppressor genes, which produces those genes which prevent cell division or cause cell death. The third group are DNA repair genes, which helps in preventing mutations that leads to skin cancer.

The UV radiations are well absorbed by the DNA and cell proteins and act as initiator as well as a promoter in the formation of mutagenic photoproducts inside DNA (Cooke et al., 2003). These photoproducts are formed between the adjacent thymine (T) and cytosine (C) base pairs and between the pyrimidine base pairs. These dimmers formed are known as cyclobutane dimmers and the pyrimidine (6-4) dimmers respectively (Rastogi et al., 2010). The 6-4 photoproducts are less mutagenic than CPD which is also termed as "hot spot mutation". In addition, they also interfere with the immune system of the body, cause immnosuppression and activate those genes which are directly responsible for causing mutation in DNA. The cells of the skin adopt DNA repair mechanisms to prevent mutation (Ouhtit and Ananthaswamy, 2001). It is an important step in decreasing the susceptibility of acquiring skin cancer. If the degree of DNA damage is not high, then the cell returns to normal state through the repair process but if the degree of damage is higher, then it cannot be repaired by DNA repair mechanism and undergoes apoptosis. Thus, the body prevents the proliferation of cells in the form of tumors. Role in Nucleotide excision repair (NER) in UV radiation associated damage repair process is highly significant (Teiti et al., 2011). There are two major pathways of NER called transcription-coupled repair (TCR) and global genome repair (GGR) which removes pyrimidine dimers in DNA, replacing the damaged site with a newly synthesized polynucleotide (Story et al., 1997). Here the noteworthy thing is that the TCR is more rapid in action than the GGR in removing damage from genes, regulated by p53 gene.

2. Matrix metalloproteinase enzyme system and novel inhibition strategy:

The degeneration of extracellular matrix (ECM) involves the activity of various protease enzymes. The prime focus moves toward the family of multidomain zinc and calcium dependent endopeptidase activity at neutral pH responsible for the damage caused to skin connective tissue (the dermis) (Quan et al., 2009). The typical family of MMPs can be divided into eight classes based on their structure. The common feature of all the MMPs is that they contain a N-terminal predomain followed by a prodomain which remains in close association with Zinc and calcium and catalytic domains. The catalytic domain consists of a zinc binding moiety having specific action. Other similar features found in all MMPs to be their collagen binding domain (CBD) which is involved in binding of collagen, elastin, fatty acid, etc. (Morrison et al., 2009; Langton et al., 2010).

The most important structural characteristics of MMPs are there trans-membrane domain which firmly anchors them to the cell surface. Each and every MMPs involves a process of regulation of activity exhibited by them. These fundamental processes are Secretion, Transcription, Pro-enzyme activation and activity