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Cancer growth regulation by 4-hydroxynonenal

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ABSTRACT

While reactive oxygen species (ROS) gain their carcinogenic effects by DNA mutations, if generated in the vicinity of genome, lipid peroxidation products, notably 4-hydroxynonenal (HNE), have much more complex modes of activities. Namely, while ROS are short living and have short efficiency distance range (in nm or μm) HNE has strong binding affinity for proteins, thus forming relatively stable adducts. Hence, HNE can diffuse from the site or origin changing structure and function of respective proteins. Consequently HNE can influence proliferation, differentiation and apoptosis of cancer cells on one hand, while on the other it can affect genome functionality, too. Although HNE is considered to be important factor of carcinogenesis due to its ability to covalently bind to DNA, it might also be cytotoxic for cancer cells, as well as it can modulate their growth. In addition to direct cytotoxicity, HNE is also involved in activity mechanisms by which several cytostatic drugs and radiotherapy exhibit their anticancer effects. Complementary to that, the metabolic pathway for HNE detoxification through RLIP76, which is enhanced in cancer, may be a target for anti-cancer treatments. In addition, some cancer cells can undergo apoptosis or necrosis, if exposed to supraphysiological HNE levels in the cancer microenvironment, especially if challenged additionally by pro-oxidative cytostatics and/or inflammation. These findings could explain previously observed disappearance of HNE from invading cancer cells, which is associated with the increase of HNE in non-malignant cells close to invading cancer utilizing cardiolipin as the source of cancer-inhibiting HNE.

1. Introduction

Pathophysiological relevance of oxidative stress (OS) and lipid peroxidation (LPO) in fundamental cellular processes and in particular in growth regulation is nowadays revealed. Namely, increasing amount of research data gives evidence not only for their pathological, but also for physiological effects. In addition, we learned that neither low levels nor high levels of pro- and anti-oxidants are desirable, as was well presented by Niki who suggested that “bad stress” should be referred to as distress and “good one” as eustress [1]. Eustress describes positive effects of stress, or hormesis, where adaptation and increased resistance are positive consequences of the low or medium levels of stress. On the other hand, distress corresponds to high stress levels being associated with inability of the cell to repair adequately all the damage that consequently leads to cell death.

The line between good and bad stress is rather thin and easily broken allowing the aggressive OS to achieve its undesirable effects including carcinogenesis. Indeed, one of the hallmarks of cancer cells is deregulated redox homeostasis resulting in excess of reactive oxygen species (ROS) production that promotes malignant transformation of the stressed cells and support cancer growth and dissemination. In order to prevent ROS-induced toxicity, cancer cells alter metabolic pathways and increase their antioxidative defense ability [2]. Although it is commonly considered that ROS gain their carcinogenic effects by induction of the DNA mutations, implicating excess of ROS being generated in the vicinity of genome, the activities of the LPO products, notably of 4-hydroxynonenal (HNE), are assumed to be much more complex. While ROS are short living and react on short efficiency distance (in nm or μm), HNE has strong binding affinity for proteins, forming relatively stable adducts. These adducts can diffuse form the site or origin changing the protein structure and function. Consequently, HNE can influence proliferation, differentiation and apoptosis of cancer cells on one hand, while on the other it can affect genome functionality, too. Therefore, main goal of this paper is to give a short, but comprehensive overview on the effects of HNE in cancer growth control.

2. HNE production and reactivity

HNE is one of the most studied end-products of LPO, generated by oxidative degradation of n6- polyunsaturated fatty acids (PUFAs) such as arachidonic and linoleic acid [3]. It is highly electrophilic molecule

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and, as such, can easily react with cellular macromolecules: proteins, DNA and phospholipids. The reactive nature of HNE is due to its three functional groups: C2=C3 double bond, C1 carbonyl group, and C4 hydroxyl group. Reactions of the C=C double bond include Michael additions, where nucleophiles such as cysteine, lysine, histidine and guanine are added to HNE, as well as reduction and epoxidation. Carbonyl group can be targeted to Schiff-base formation with primary amines (e.g. lysine), can form (thio-)acetals when HNE reacts with alcohols or thiols. In addition, HNE can be oxidized by aldehyde dehydrogenase (ALDH) to produce 4-hydroxy-nonenoic acid, or can be reduced by alcohol dehydrogenase or aldose reductase. Hydroxyl group can be oxidized to a ketone but may also be phosphorylated [4,5].

3. Lipid peroxidation and cancer-specific (dis)appearance of HNE

The first data mentioning the toxicity of LPO end products appeared in the seventies [6]. Further genotoxicity of these products was described at the beginning of nineties [7,8]. Consequently, LPO end products were intensively studied and were referred as “second toxic messengers of free radicals” emphasizing their role in the toxicity of free radical processes [3]. Afterwards the perception of HNE as “toxic only” changed and the research focus moved toward its role as a growth regulating and signaling molecule in the biological events such as chemotaxis, signal transduction, gene expression, cell proliferation, differentiation and cell death [9–11]. These processes are crucial in regulation of the normal cell behavior, hence their modulation by HNE can interfere with the control of normal or malignant cell growth and metabolism thereby supporting and/or inhibiting development of tumors. The relevance of HNE in modulation of cancer growth can be easily perceived by its interactions with signaling pathways modulating the Hanahan and Weinberg's hallmarks of cancer [12] as shown in Fig. 1.

Early data on HNE as growth modulating factor were provided by *in vitro* experiments using cancer cells [10], which lead to conclusion that regulating effects of HNE are due to its interaction with cytokines and related humoral growth factors and/or due to its influence on cellular autocrine growth (dis)regulation. Accordingly, it was of interest to define synthesis and accumulation of HNE within normal and malignant cells and its interference with growth regulating cytokines *in vivo*, especially in case of cancer. Early studies using monoclonal antibodies specific for the HNE-protein conjugates showed differences of the HNE appearance between normal kidney tissue and renal tumors, with variations in intensity depending on tumor type and the type of kidney cells analyzed [13]. Moreover, a decrease of the HNE content in colon carcinoma tissue was revealed by Biasi et al. compared to normal colon tissue [14], with exception of the highest tumor grade. In correlation with reduced HNE levels in human colon cancer the expression of TGF-β1 was decreased indicating possible regulatory role of HNE in colon carcinogenesis. However, the pattern of HNE histological appearance is not universal but is dependent on the histological origin of cancer [11]. Thus, in brain tumors the amounts of HNE-protein adducts were found to increase with increasing malignancy of these tumors [15,16].

It was also observed that the presence and localization of HNE in normal tissues may reflect its physiologic roles as well as its causative involvement in the early onset of pathological processes. In favor to this is the change of subcellular location of HNE observed in patients with duodenal ulcer, where HNE was found not only in the cytoplasm of the glandular cells in gastric mucosa, but also in the nuclei of these cells [17]. Even further, in support of this finding is the Long-Evans Cinnamon (LEC) rat model of hepatitis and liver carcinogenesis based on the hepatic accumulation of copper [18]. These animals spontaneously develop jaundice and acute hepatitis which further deteriorates into onset of liver carcinoma. The presence of HNE in the nuclear region of liver cells in the early stages of such carcinogenesis implicates its involvement in liver cancer initiation [18]. In order to get better insight on the pathways by which HNE may regulate cancer initiation, growth and malignancy, we present here the essential signaling pathways of cell proliferation and adaptation to the stress conditions that are sensitive to HNE biological activities in the HNE concentration-dependent manner.

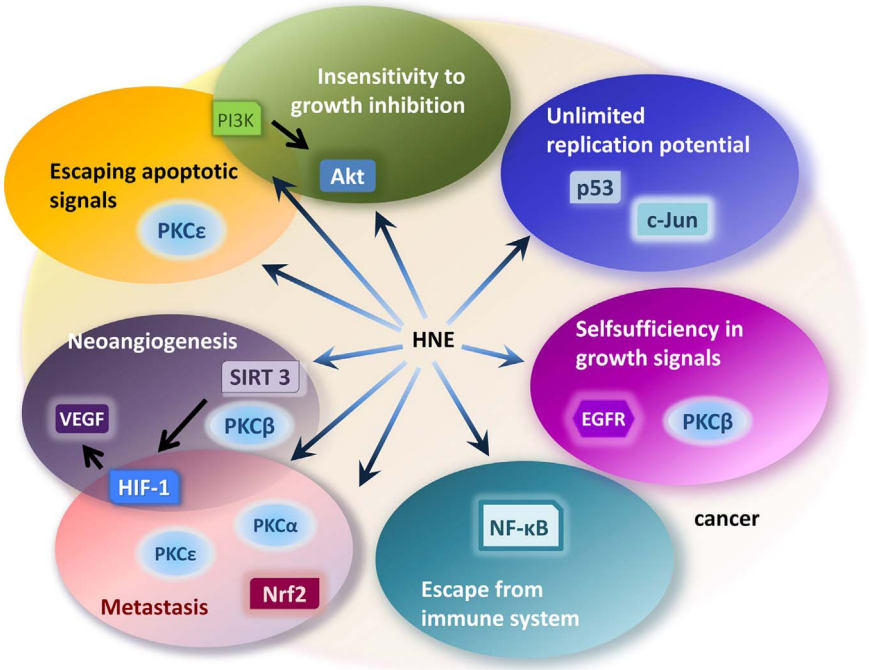

Fig. 1. Hallmarks of cancer and HNE. The scheme presents seven hallmarks of cancer with signaling molecules modulated by HNE. Weinberg's hallmarks of cancer [12] reflect changes in expression and activity of great number of signaling molecules. Here, only examples of affected signaling molecules are shown as their common feature is susceptibility for the HNE-driven bio-modulation.