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Review

Potential role of *N*-myristoyltransferase in cancer

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Abstract

Colorectal cancer is the second leading cause of malignant death, and better preventive strategies are needed. The treatment of colonic cancer remains difficult because of the lack of effective chemotherapeutic agents; therefore it is important to continue to search for cellular functions that can be disrupted by chemotherapeutic drugs resulting in the inhibition of the development and progression of cancer. The current knowledge of the modification of proteins by myristoylation involving myristoyl-CoA: protein *N*-myristoyltransferase (NMT) is in its infancy. This process is involved in the pathogenesis of cancer. We have reported for the first time that NMT activity and protein expression were higher in human colorectal cancer, gallbladder carcinoma and brain tumors. In addition, an increase in NMT activity appeared at an early stage in colonic carcinogenesis. It is conceivable therefore that NMT can be used as a potential marker for the early detection of cancer. These observations lead to the possibility of developing NMT specific inhibitors, which may be therapeutically useful. We proposed that HSC70 and/or enolase could be used as an anticancer therapeutic target. This review summarized the status of NMT in cancer which has been carried in our laboratory.

Keywords Lipid modification; Myristoylation; Myristoyltransferase; Heat shock cognate protein 70; Inhibitors; Cancer

Contents

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1. Introduction

Colorectal cancer is a major cause of death, particularly in the western world, leading to 400,000 deaths each year. Of the patients, 30% have advanced disease at presentation, either locally or at distant sites and chemotherapy in this setting has an established role in improving survival and palliating symptoms. Approximately 50% of those patients, who were initially believed to be cured by surgery, relapse subsequently and die of their disease. In recent years significant progress has been made in understanding the nature of the human genome and the role that genes and their related proteins play in both normal and diseased cells. Many cancers are caused by the mutation of certain genes or lack of gene functions. The introduction of those genes into cancer cells where the gene function has been compromised can work to restore gene function and stop tumor progression [1–5]. The modifications of proteins by phosphorylation or by the attachment of carbohydrate, acetyl, formyl or nucleoside moieties are well established as important in cellular regulation processes. Recently, the role of lipid modification of proteins and protein function is receiving attention. The main purpose of this review article is to summarize the importance of *N*-myristoyltransferase (NMT) that has been carried out in our laboratory. Excellent reviews on this subject have been published previously [6–15].

2. Lipid modifications

Lipid attachment is one of the most common post-translational modifications in eukaryotic cells [7]. The process is sequence specific and involves several enzymatic steps. This modification takes place either at or near the amino terminus or the carboxy terminus of the protein. There are four broad types of lipid modifications with specific functional properties which have been classified according to the identities of the attached lipid. These include: 1, myristoylation which represents the attachment of myristate (C14) via a stable amidic linkage to an amino-terminal glycine residue and irreversible modification; 2, palmitoylation is the attachment of palmitate (C16) through an ester or thioester bond to a serine (threonine) or cysteine residue, respectively near the amino terminus and is reversible modification; (3) prenylation is a lipid modification involving the covalent addition of either farnesyl (C15) or geranylgeranyl (C20) isoprenoids to conserved cysteine residues at or near the carboxy terminus of proteins; and (4) a glycosylphosphatidylinositol anchor which is a complex structure involving both lipids and carbohydrate molecules that is reversibly attached to some proteins to target them to the cell membrane.

3. Myristoylation

Recently, there has been a major emphasis on understanding the lipidic modifications of proteins. Protein *N*-myristoylation is one such lipidic modification which refers to the covalent attachment of myristate, a 14