Chapter 10

Cancer Metabolomics and Drug Discovery

Cancer Metabolic Phenotype

Exploiting the Cancer Metabolome in Drug Discovery

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Summary

Cancer cells exhibit surprisingly uniform metabolic abnormalities, termed the cancer metabolic phenotype. We define six classes of mechanism giving rise to this phenotype: mechanisms associated with (1) oncogenesis; (2) rapid reproduction; (3) stress responses; (4) invasiveness and metastasis; (5) resistance to host immune surveillance; (6) resistance to therapy. Classes 1 and 2 are constitutive mechanisms, involved in the process of oncogenesis, whereas classes 4–6 mainly involve selection for features responsive to the tumor’s environment. We next analyze some well-known features of the tumor metabolic phenotype: the Warburg effect, aerobic glycolysis, and tumor pH. Contrary to accepted wisdom, tumors do not rely on glycolysis for their energy needs and their intracellular pH is not acidic.

The concept of the metabolome—the totality of small-molecule metabolites in a cell—has had little attention in cancer. We discuss ways in which the cancer metabolome could be investigated, by metabolic profiling, illustrated by studies on the HIF-1 pathway. Finally, we consider ways in which tumor metabolic profiling could be used in drug discovery programs: to help chose targets from functional genomic data, to refine results from conventional screens or to provide end points for focused screens and medicinal chemistry, to predict cellular and whole-organism toxicity, and to help elucidate drug mechanisms.

Key Words: Cancer; metabolic phenotype; metabolomics; NMR; drug discovery.

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135
1. INTRODUCTION

The distinctive metabolic abnormalities of cancer cells are among the most widely recognized features of the cancer phenotype, and many pharmacological and other therapies depend on them. The new science of metabolomics has opened up a novel way of looking at the tumor metabolic phenotype, one that will be exploitable in drug development. This chapter will begin by considering the basic mechanisms underlying metabolic aspects of the tumor phenotype, followed by an analysis of some of its better known features. Contrary to accepted wisdom, for instance, tumors do not rely on glycolysis for their energy needs and their intracellular pH is not acidic. We will next consider the concept of the “cancer metabolome” and ways in which it could be investigated, both in general and in a more limited way by metabolic profiling as illustrated by studies on the HIF-1 pathway. Finally, we will try to predict ways in which tumor metabolic profiling could be used to assist drug discovery.

2. THE ORIGINS OF THE CANCER CELL METABOLIC PHENOTYPE

Why do cancer cells have an abnormal metabolic phenotype? Why, indeed, should there be a characteristic cancer cell phenotype, in view of the hundred or so types of cancer, arising from malignant transformation of most types of differentiated cell? There are many reasons why the development of cancer cells channels their metabolism into characteristic phenotypic patterns. They can be loosely grouped into six classes (see Fig. 1).

2.1. Class 1: Constitutive Mechanisms Associated With Oncogenesis

Many processes have been proposed as causes of malignant transformation, but in the principal current theory, the formation of a cancer cell requires a series of mutations in the DNA sequences of its ancestral cells, either giving rise to oncogenes or impairing the action of tumor suppressor genes. The protein products of oncogenes and tumor suppressor genes tend to fall into characteristic groups. For instance, many oncogenes are growth factors, receptors, or transcription factors or are otherwise concerned in the signaling pathways involved in cell replication. The net effect of such mutations is to produce cells that continue to reproduce in the absence of external mitogenic stimulation. Other tumor suppression factors that are commonly mutated in cancer cells would normally be involved in the culling, by apoptosis, of abnormal cells. Thus, as most of these mutations are clustered in a few pathways, the resulting abnormal metabolic phenotypes will tend to be to be similar.

Genomic instability is another common, constitutive feature of cancer cells, and it results in rapid generation of a large variety of clones that are then subject to natural selection. Genomic instability (as well as aneuploidy, another putative cause of oncogenesis...

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Fig. 1. (Opposite page) Illustrative examples from the six classes of mechanism that give rise to the tumor metabolic phenotype. Class 1, oncogenesis: One or more mutations cause malignant transformation of a single cell. Class 2, rapid reproduction: Clones with metabolic phenotypes characteristic of rapid division predominate. Class 3, expression of stress response mechanisms: Stress response pathways such as HIF are activated both constitutively by oncogenic mechanisms in class 1 and in response to the environment. The figure shows the development of a glycolytic phenotype in cells too far from the nearest blood vessel to receive adequate oxygen. Class 4, invasion and metastasis: