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Mini-review

Mevalonate metabolism in cancer

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ABSTRACT

Cancer cells are characterized by sustained proliferative signaling, insensitivity to growth suppressors and resistance to apoptosis as well as by replicative immortality, the capacity to induce angiogenesis and to perform invasive growth. Additional hallmarks of cancer cells include the reprogramming of energy metabolism as well as the ability to evade immune surveillance. The current review focuses on the metabolic reprogramming of cancer cells and on the immune system's capacity to detect such changes in cancer cell metabolism. Specifically, we focus on mevalonate metabolism, which is a target for drug and immune based cancer treatment.

1. Introduction

The original hallmarks of malignant cancer as defined by Hanahan and Weinberg in 2000 included sustained proliferative signaling, evasion from growth suppressors, resistance to cell death, replicative immortality, capacity to induce angiogenesis as well as invasive growth leading to metastasis [1]. The revisited concept from 2011 contains two additional hallmarks: the reprogramming of energy metabolism and evasion from immune surveillance [2]. A reprogramming of energy metabolism in cancer cells was first described by the Nobel Prize winner Otto Warburg as early as the 1920s [3]. The phenomenon named after him refers to enhanced glycolysis, i.e. the stepwise pathway that converts glucose into pyruvate with the net generation of two molecules of ATP, in tumor cells even under normal aerobic conditions. The broad relevance of this finding is illustrated by the fact that, today almost a century after the formulation of Warburg's Hypothesis, clinical oncologists take advantage of the increased glucose uptake by cancer cells in order to detect metastases. The biologically active glucose analog fluorodeoxyglucose (FDG) serves as a tracer, which accumulates in metabolically hyperactive tumor cells. The concentrations of tracer are imaged by positron emission tomography (PET). FDG–PET combined with computed tomography (CT) giving both anatomic and metabolic information has a high sensitivity and specificity for the detection of solid cancer metastases [4].

To supply their energetic requirements by aerobic glycolysis, tumor cells rapidly convert glucose into pyruvate, which enters mitochondria, where it is introduced into the tricarboxylic acid (TCA, citrate or Krebs) cycle and oxidized to acetyl-Coenzyme A (acetyl-CoA). Another feature of reprogrammed cancer cell metabolism is the increased export of acetyl-CoA into the cytosol, where it serves as a building block for mediators of cell growth and proliferation. In this manner, acetyl-CoA is increasingly made available for mevalonate metabolism (Fig. 1).

The mevalonate pathway for cholesterol biosynthesis and protein prenylation has been implicated in various aspects of cancer development and progression [5,6]. Hyperactivity of the mevalonate pathway for protein prenylation, which has been reported to promote cell transformation and malignancy [7,8], represents acute biohazard and therefore requires tight surveillance. It becomes increasingly apparent that the immune system performs such an inherent surveillance of stressed cells, a phenomenon that has been referred to as lymphoid stress surveillance [9]. γδ T lymphocytes can kill cells with hyperactive mevalonate metabolism by specifically recognizing intermediates of the pathway and can thereby eliminate newly formed cancer cells. Moreover, reciprocal interactions between γδ T lymphocytes and dendritic cells promote the maturation of dendritic cells and the subsequent initiation of adaptive immunity [10]. If the immune system fails to fulfill its surveillance function, therapeutic intervention with drugs that target the mevalonate pathway is likely to be beneficial. Important classes of drugs such as the nitrogen-containing bisphosphonates (N-BPs) or the statins inhibit the pathway at different levels and thus exhibit antitumor effects. While statins inhibit the first committed step and thereby suppress the entire pathway, N-BPs act downstream and exhibit a more complex pattern of action as they cause both the downstream depletion as well as the upstream accumulation of mevalonate metabolites [6]. Importantly, both classes of drugs not only have direct antitumor effects but also exert indirect effects by stimulating similar but not identical inflammatory and immune responses, which may contribute to their therapeutic efficacy.

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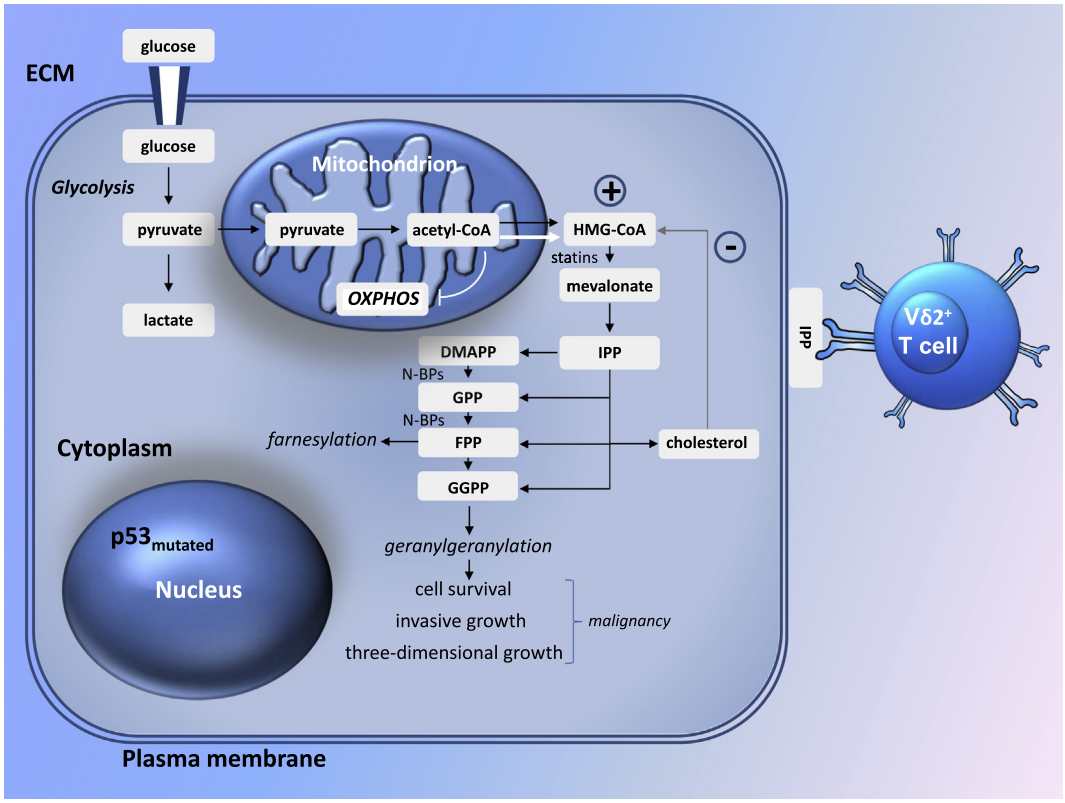

Fig. 1. Metabolic reprogramming of tumor cells includes upregulation of aerobic glycolysis (Warburg effect) at the expense of oxidative phosphorlyation (OXPHOS). Glycolysis in tumor cells generates pyruvate, which is either converted to lactate or introduced into the TCA (citrate or Krebs) cycle. However, mitochondrial oxidation is incomplete and leads to an enhanced export of acetyl-CoA in the cytosol. Cytosolic acetyl-CoA serves as a building block for anabolic reactions that promote cell growth and proliferation. Acetyl-CoA can be used to form HMG-CoA and thus to initiate mevalonate metabolism, which is enhanced by mutated p53. Statins inhibit HMG-CoA reductase, the first committed step of the mevalonate pathway. Nitrogen-containing bisphosphonates (N-BPs) inhibit FPP synthase. FPP and GGPP are the lipid donor substrates for protein farnesylation and geranylgeranylation, respectively. FPP is the precursor for cholesterol biosynthesis and cholesterol acts as a feed-back inhibitor of HMG-CoA reductase. The intermediate IPP, which is also produced by many bacteria and parasites, can be recognized by γδ T cells.

The present review highlights the role of mevalonate metabolism in cancer biology as well as in cancer immune surveillance and summarizes evidence, which emphasizes the mevalonate pathway as an important therapeutic target.

2. The mevalonate pathway for steroid biosynthesis and protein prenylation

Decarboxylation of glycolytically derived pyruvate generates acetyl-CoA, which is the precursor for several lipid building blocks. Two acetyl-CoA molecules can be condensed by thiolase to create acetoacetyl-CoA. HMG-CoA synthase condenses acetoacetyl-CoA with another acetyl-CoA to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). In the first committed step of the pathway (Fig. 1), which is inhibited by the statins, HMG-CoA reductase converts HMG-CoA into mevalonate (mevalonic acid) [11]. Two sequential phosphorylations generate mevalonate diphosphate (or pyrophosphate), which is decarboxylated to form isopentenyl pyrophosphate (IPP). An isomerase catalyzes the interconversion of IPP and its isomer dimethylallyl pyrophosphate (DMAPP), which both represent isoprenoid precursor molecules for diverse classes of cellular products (Table 1). Farnesyl pyrophosphate (FPP) synthase, the target of the N-BPs, condenses DMAPP with one IPP molecule to form geranyl pyrophosphate (GPP) as well as GPP with a second IPP to form FPP. FPP finds itself at an important branching point and may, for instance, serve as a precursor for cholesterol and steroid biosynthesis or contribute to posttranslational protein modifications such as glycosylation and prenylation. Enhanced glycolysis in cancer cells also generates ATP molecules, which are required for the pyrophosphorylation of mevalonate.

In the cholesterol/steroid biosynthesis branch, squalene synthase catalyzes in an NADPH-dependent fashion a two-step reaction, in which two identical molecules of FPP are converted into squalene. Squalene oxidation followed by cyclization leads to lanosterol, which can be further converted to cholesterol. Feedback inhibition by cholesterol and isoprenoid intermediates of the mevalonate pathway controls HMG-CoA reductase [11,12]. In animal cells all steroids are made from lanosterol.

Breast cancer and prostate cancer, which are the two most common invasive cancers in women and men, respectively, are typically steroid hormone-dependent [13]. The sex steroid hormones oestrogen and androgen are well established as key drivers of these two types of cancer. Many therapeutic strategies have therefore been designed to either inhibit steroid biosynthesis or block receptor function, collectively referred to as hormone therapy. Unfortunately, most breast and prostate tumors that initially respond to hormone therapy later on reinitiate growth in a hormone-independent fashion. Such hormone-refractory cancers are deemed incurable.

In the prenylation branch of the mevalonate pathway, GGPP synthase condenses FPP with yet another IPP to form GGPP. FPP and GGPP can now be used as activated isoprenoid substrates in a posttranslational modification, which is referred to as protein prenylation [14]. The enzymatic transfer of farnesyl- or geranylgeranyl moieties to proteins enables these proteins to attach to cell membranes and to carry out their biological function. Many members of the Ras superfamily of small GTPases, which comprises more than 150 human members [15] depend on prenylation for

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