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Review

Regulation of mevalonate metabolism in cancer and immune cells

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ABSTRACT

The mevalonate pathway is a highly conserved metabolic cascade and provides isoprenoid building blocks for the biosynthesis of vital cellular products such as cholesterol or prenyl pyrophosphates that serve as substrates for the posttranslational prenylation of numerous proteins. The pathway, which is frequently hyperactive in cancer cells, is considered an important target in cancer therapy, since prenylated members of the Ras superfamily are crucially involved in the control of proliferation, survival, invasion and metastasis of tumour cells. Upstream accumulation and downstream depletion of mevalonate pathway intermediates as induced for instance by aminobisphosphonates translate into different effects in cancer and immune cells. Thus, mevalonate pathway regulation can affect tumour biology either directly or exhibit indirect antitumour effects through stimulating cancer immune surveillance. The present review summarizes major effects of pharmacologic mevalonate pathway regulation in cancer and immune cells that may collaboratively contribute to the efficacy of cancer therapy.

1. Introduction

Isoprenoids, which are the oldest known biomolecules, are synthesized ubiquitously through condensations of the five-carbon compound isopentenyl pyrosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP) [1,2]. In mammals and yeasts, IPP is generated in a highly conserved metabolic cascade referred to as the mevalonate pathway, which was first discovered in the 1950s. Seminal work by Goldstein and Brown focused on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase as the rate-limiting enzyme in cholesterol biosynthesis [3]. However, additional branches of the pathway exist that lead, for instance, to the posttranslational prenylation of multiple members of the RAS superfamily [4–6]. Imbalances of mevalonate metabolism are now known to be causative of high-prevalence lifestyle diseases including cardiovascular disease and cancer and have established the mevalonate pathway as an important therapeutic target. HMG-CoA reductase is the target of the widely prescribed cholesterol-lowering drugs collectively known as the statins. In addition to hypercholesterolemia, statins have also been implicated in the treatment and prevention of cancer [7,8]. Farnesyl pyrophosphate (FPP) synthase, another key enzyme of the pathway, is the target of the nitrogen-containing bisphosphonates (N-BPs), a class of bone anti-resorptive drugs for the treatment of osteoporosis and metastatic bone disease. Although statins and N-BPs are already well established as antitumour agents, the recent findings that statin-mediated inhibition of the mevalonate pathway can profoundly affect tumour biology [9] and that both, statins and N-BPs, can mediate inflammasome-dependent innate immune activation [10,11] reinforce the view that the mevalonate pathway is an important target for cancer therapy.

2. The mevalonate pathway: a factory of vital building blocks

The mevalonate pathway provides isoprenoid building blocks for rather diverse classes of end products (Fig. 1). These include cholesterol, steroids, bile acids, vitamin D, dolichols, haem A, ubiquinone and isopentenyl adenine [3,12,13]. In addition, FPP and geranylgeranyl pyrophosphate (GGPP) serve as donor substrates in a posttranslational modification process of cellular proteins, which is referred to as protein prenylation [4,6,14] (Fig. 2). In the first committed step of the pathway, HMG-CoA reductase converts HMG-CoA to mevalonate. HMG-CoA reductase is regulated through feedback mechanisms [15]. Full suppression of the reductase occurs in the presence of cholesterol, which is normally derived exogenously from plasma low density lipoprotein (LDL), and if an excess of mevalonate is concomitantly supplied. Since HMG-CoA reductase is the rate-controlling step of cholesterol biosynthesis, its inhibition by statins represents an effective strategy to lower cholesterol levels in patients with cardiovascular disease [3]. Mevalonate is further metabolized to IPP and its isomer DMAPP. FPP synthase, the target of the N-BPs [5,16], catalyzes sequential condensation reactions of DMAPP with two units of IPP to form FPP. GGPP synthase catalyzes yet another condensation reaction to form GGPP

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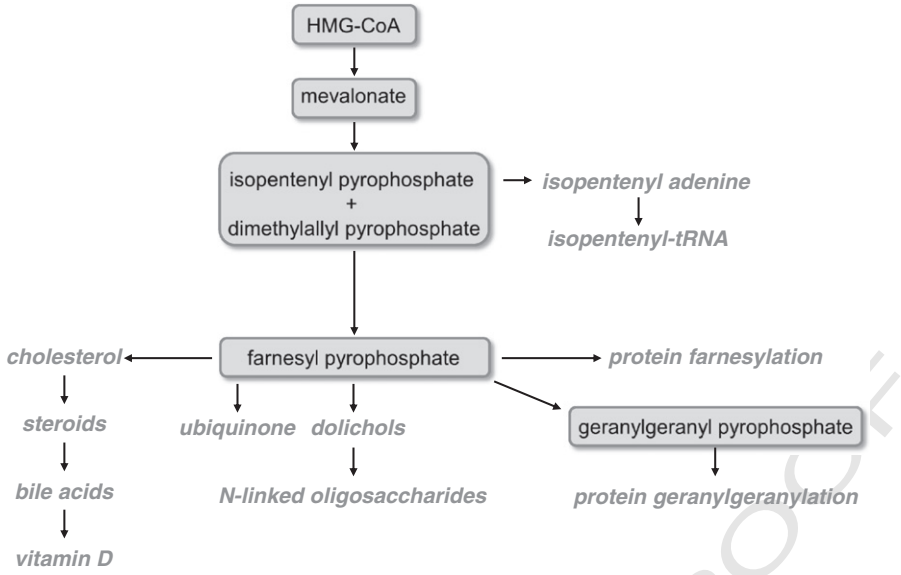

Fig. 1. Mevalonate-derived products. The mevalonate pathway generates isoprenoid building blocks (isopentenyl pyrophosphate — IPP, dimethylallyl pyrophosphate — DMAPP, farnesyl pyrophosphate — FPP) for diverse classes of end products. Isopentenylation of tRNAs serves to optimize codon–anticodon fit in the ribosome and to promote translational fidelity. Cholesterol is an essential structural component of mammalian cell membranes and determines fluidity and permeability. In addition, cholesterol is a precursor in the biosynthesis of steroid hormones, bile acids and vitamin D. Ubiquinone (also known as coenzyme Q10) is a component of the electron transport chain in the respiratory chain and participates in aerobic cellular respiration, which generates energy in the form of ATP. Dolichol phosphate serves as a membrane anchor during formation of N-linked oligosaccharides. Many members of the Ras superfamily of small GTPases are prenylated (farnesylated, geranylgeranylated, or both). Haem A (or heme A), an iron-chelating porphyrin, which also participates in electron transport, is also farnesylated. The farnesyl side chain of haem A is considered to be important in the conservation of energy during oxygen reduction by cytochrome c oxidase.

(Figs. 2 and 3B). Both, FPP and GGPP represent activated isoprenoid units that can be posttranslationally transferred to proteins (protein prenylation) [4,6]. Many members of the Ras and Rho family of small guanosine triphosphatases (GTPases) are prenylated and use the lipidated hydrophobic domain of the prenyl residue for membrane attachment, which is often a prerequisite for their biological function [6]. Farnesyltransferase, geranylgeranyltransferase I and geranylgeranyltransferase II are the three known enzymes, which can catalyze protein prenylation. Farnesyltransferase (FTase) uses the 15-carbon molecule FPP as a prenyl donor to transfer a farnesyl group to the C-terminal CaaX motif (C is cysteine, A is usually an aliphatic residue, and X is any amino acid). Geranylgeranyltransferases (GGTases) use the 20-carbon compound GGPP to transfer a geranylgeranyl moiety to their target proteins (Fig. 2). GGTase I has been shown to prenylate some of the substrates of FTase and vice versa.

Many members of the Rab family of Ras-related G-proteins are also prenylated, although they lack the CaaX sequence. Prenylation of Rab proteins, which do not have a consensus sequence, such as the CaaX box, but instead often contain a CC or CXC C-terminal sequence, is catalyzed by a distinct Rab GGTase (= GGTase 2). A Rab escort protein (REP) binds Rab proteins through these more conserved regions and presents them to the Rab GGTase, which often transfers two geranylgeranyl groups to the C-terminal cysteines of Rab proteins resulting in doubly prenylated Rab proteins. Double geranylgeranylation appears to be prerequisite for specific membrane targeting since single prenylation results in mistargeting to other membranes [17,18].

3. Inhibition of mevalonate metabolism: effects on tumour biology

Statins and N-BPs represent two important classes of mevalonate pathway inhibitors, which are currently available for clinical use. In 1975 Akira Endo discovered a potent HMG CoA reductase inhibitor (compactin) as natural product of certain molds (*Penicillium citrinum*), which became the founding member of the statin family (mevastatin) [19]. However, in animal studies mevastatin turned out to be too toxic. The next and clinically more successful candidate (mevinolin) was isolated from the fermentation broth of *Aspergillus terreus* and later became known as lovastatin. Atorvastatin (marketed as Lipitor) is among the best-selling pharmaceuticals in history. The discovery of their ability to induce apoptosis in a variety of tumour cells by specific inhibition of HMG-CoA reductase established statins as potential anticancer agents [20]. Downstream depletion of geranylgeranyl pyrophosphate, which prevents protein prenylation, at least partially accounts for the pro-apoptotic activity of statins and inhibition of Rho geranylgeranylation (rather than Ras farnesylation) seems to be responsible for the observed anticancer effect of statins [5,20]. Prompted by such promising preclinical observations, clinical trials have been conducted. However, mixed clinical responses in early phase 1/2 trials emphasized the importance of reliable markers for the subset of patients that may really benefit from statin anticancer effects [21]. Another piece of evidence for a role of statins as antitumour agents is provided by epidemiologic data, which suggested that statins can lower the risk of certain cancers by up to 50% [22,23].

Freed-Pastor et al. have recently provided new data, which confirm the importance of the mevalonate pathway as a therapeutic target [9]. The mutant form of p53, which is present in more than 50% of all human cancers, was shown to significantly upregulate mevalonate pathway activity in cancer cells. Increased mevalonate metabolism resulting in enhanced protein prenylation obviously contributes to the maintenance of the malignant phenotype of cancer cells, which is characterized by three-dimensional growth, invasive growth and prolonged survival. Intriguingly, simvastatin used at clinically relevant concentrations could reverse these features of malignancy in cancer cells expressing a single mutant p53 allele and a similar reversion of the malignant phenotype could be achieved, when endogenous mutant p53 was targeted and depleted by short hairpin RNA. Together these data indicated that enhanced mevalonate metabolism induced by mutant p53 promotes malignant transformation. To identify the responsible branch of the mevalonate pathway, the authors performed

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