REVIEW ARTICLE

Specific increase in caspase-1 activity and secretion of IL-1 family cytokines: a putative link between mevalonate kinase deficiency and inflammation

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ABSTRACT. The mevalonate kinase deficiency (MKD), including hyperimmunoglobulinemia D periodic fever syndrome (HIDS) and the more severe mevalonic aciduria are rare, autosomal recessive, autoinflammatory diseases belonging to the hereditary periodic fever (HPF) family. Other members include: familial mediterranean fever (FMF), the cryopyrin-associated periodic syndromes (CAPS) and TNFR-associated periodic syndromes (TRAPS). MKD is caused by mutations in the gene encoding mevalonate kinase (MK), an enzyme of the cholesterol pathway, leading to its inactivation. The molecular mechanisms linking MKD and abnormalities of isoprenoid biosynthesis to cytokine production and inflammation have yet to be fully elucidated. Statins, which are extensively prescribed for lowering cholesterol, are potent inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase, the enzyme directly upstream of MK. In this review, we discuss recent reports demonstrating that *in vitro* inhibition of the mevalonate pathway by statins specifically increases the production, by activated monocytes, of cytokines of the IL-1 family, by enhancing caspase-1 activity, the enzyme responsible for IL-1β and IL-18 maturation. The molecular mechanisms involve geranylgeranylation and the enhancement of the activity of G proteins such as Rac-1. Interestingly, activated fibroblasts from MKD patients secrete more IL-1β than fibroblasts from healthy donors. Taken together, these data highlight the specific enhancement of the IL-1 family of cytokines, the maturation of which is caspase-1-dependent in MKD. Finally, the spectacular decrease in febrile attacks in patients with severe HIDS under IL-1 receptor antagonist (anakinra) treatment, reinforces this hypothesis. Deregulated caspase-1 activation could be responsible for the inflammatory component of MKD, thereby mechanistically linking MKD to FMF and CAPS through cytokines of the IL-1 family.

Keywords: caspase-1, mevalonate kinase deficiency, HIDS, IL-1 family cytokines

Hyperimmunoglobulinemia D, periodic fever syndrome (HIDS; OMIM #260920) and the more severe mevalonic aciduria (MA; OMIM #310377) are rare diseases caused by recessive mutations in the *MVK* gene [1, 2] encoding mevalonate kinase (MK), an enzyme of the mevalonate pathway, which is upstream of cholesterol biosynthesis *(figure 1)*. Mutations in *MVK* lead to minimal (< 10%) or undetectable MK activity [1-4]. Phenotypic overlap between HIDS and MA provides evidence of a phenotypic continuum between both diseases [5], which have therefore become collectively known as mevalonate kinase deficiency (MKD). MKDs are autoinflammatory diseases belonging to the family of hereditary periodic fever (HPF), including familial Mediterranean fever (FMF; OMIM #249100), chronic neurologic cutaneous and articular (CINCA) syndrome (also called neonatal-onset multi-system inflammatory disease (NOMID) (OMIM #607115), Muckle-Wells syndrome (MWS, OMIM #191900), familial cold autoinflammatory syndrome (FCAS; OMIM #120100), and tumor necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS; OMIM #142680) *(table 1)*.

Most of the HPFs are linked to disorders in the secretion and/or signalling of pro-inflammatory cytokines. In TRAPS, the mutation in *TNFRSF1A* (12p13.2) is associated with a defect in the TNFR1 shedding process, leading to a reduction in circulating TNFR1, and increased

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cell surface expression, both thought to result in increased signalling through TNFR1 [6]. However, many mutations in TRAPS do not involve this process [7]. In addition, recent clinical studies have shown that anti-TNF (infliximab) treatment of patients with TRAPS is able to trigger inflammation [8], whereas a beneficial response to IL-1ra (anakinra) treatment is reported in TRAPS [9-11]. This suggests that the pathophysiology of TRAPS is not entirely clear and that IL-1 might also play a key role in this autoinflammatory disease.

FMF is caused by mutations in the *MEFV* gene (16p13) encoding pyrin/marenostrin [12, 13], while *CIAS1* (1q44), the gene encoding cryopyrin/NLRP3, is mutated in MWS, CINCA, NOMID and FCAS, which are therefore grouped as the cryopyrin-associated periodic syndromes (CAPS) [14, 15]. The resulting mutated pyrin and cryopyrin lead to dysregulated maturation of IL-1β [16, 17]. Cryopyrin is implicated in a multiprotein complex, the NLRP3 inflammasome, which promotes the activation of caspase-1, the maturation enzyme of pro-inflammatory members of IL-1 family cytokines, in particular IL-1β and IL-18 *(figure 1)*. Indeed, IL-1β and IL-18 have the common feature of being synthesized as inactive pro-cytokines that require proteolytic processing by caspase-1 for maturation into the active form [18, 19]. The implication of pyrin in inflammasome oligomerisation is less clear. The inhibition of inflammasome assembly through an interaction of pyrin with the protein ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain) has been suggested. This interaction, through their respective pyrin domain (PYD), could prevent the binding of cryopyrin to ASC, leading to the inhibition of the inflammasome heteromerisation [20, 21]. On the other hand, it has been suggested that pyrin, like cryopyrin, is also able to form an inflammasome complex involving ASC and procaspase-1, leading to caspase-1 activation and IL-1β processing [22]. In any case, the exact mechanism of action of pyrin remains incompletely understood.

In contrast to TRAPS, FMF, and CAPS, in which at least some genetic mutations seem to be directly linked to inflammation *via* TNFR hyperactivation or caspase-1 activation [23], the molecular mechanisms linking MKD and abnormalities of isoprenoid biosynthesis to cytokine production and inflammation remain to be fully elucidated.

Abbreviations

CAPS	cryopyrin-associated periodic syndrome
CINCA	chronic neurologic cutaneous and articular syndrome
FCAS	familial cold autoinflammatory syndrome
FMF	familial mediterranean fever
FPP	farnesyl-pyrophosphate
FTI	farnesyltranferase inhibitor
GGPP	geranylgeranyl-pyrophosphate
GGTI	geranylgeranyltransferase inhibitor
HIDS	hyper IgD and periodic fever syndrome
HMGR	3-hydroxy-3-methylglutaryl-CoA reductase
HPF	hereditary periodic fever
Ig	immunoglobulin
IL	interleukin
LPS	lipopolysaccharide
MA	mevalonic aciduria
MK	mevalonate kinase
MKD	mevalonate kinase deficiency
PBMC	peripheral blood mononuclear cell
TNF	tumor necrosis factor
TNFR	TNF receptor
TRAPS	TNFR-associated periodic syndrome

MEVALONATE KINASE DEFICIENCY

Beyond the severe developmental and neurological features of MA, MKD patients suffer from recurrent episodes of fever with no clearly identified origin. Febrile attacks that occur every two to eight weeks and last two to seven days are commonly associated with abdominal pain, diarrhea, vomiting, hepatosplenomegaly, lymphadenopathy, arthralgia, skin rashes and headache [24], and a phenotypic continuum has been demonstrated between HIDS and MA [5]. HIDS is also characterized by elevated levels of IgD (above 150 mg/L) [25], although a number of patients do have normal values, notably at the beginning of the disease, that persist independently of the attacks. Drenth *et al.* have shown that IgD is a potent inducer of TNF-α, IL-1β and IL-1ra by cultured PBMCs, and therefore hypothesized that IgD could be responsible for the inflammatory symptoms of HIDS, in spite of the lack of correlation with clinical events [26]. In any event, the mechanism of action of IgD remains obscure. Receptors for IgD have been reported on T cells, but their genes remain to be cloned, and their full molecular characterization is still imprecise [27].

Independently, we have reported that elevated serum IgD levels are also detected in the severe forms of FMF [28] or TRAPS [29]. A wide and non-Gaussian distribution of IgD concentration is observed in the serum of patients, as previously described for healthy subjects [30]. Note that 3.2% of healthy subjects had IgD serum levels above 150mg/l. In any case, serum levels of IgD were strongly enhanced in unrelated patients with TRAPS, when compared to controls ($p < 0.0001$), and the percentage of patients with serum levels greater than 150 mg/L were increased from 3.2 to 31.2% in TRAPS. Regarding FMF, we found increased IgD concentrations in the serum of patients with undetected or only one mutation in the *MEFV* gene, and this enhancement was more pronounced ($p < 0.0001$) in patients carrying homozygous or double heterozygous *MEFV* mutations, especially M694V homozygotes [28].

Although not exclusive to HIDS and HPF in general, the presence of high levels of IgD is a common factor of these diseases, and is generally considered as a nonspecific marker of the disease [31]. A very recent study showed that patients with HIDS, TRAPS and MWS had increased numbers of circulating and mucosal IgD+ IgM- plasmablasts than healthy donors [32]. These patients also had fewer circulating, but more mucosal "IgD-armed" basophils and after IgD crosslinking, IL-3-treated basophils from healthy donors released both IL-1β and TNF. The authors suggested a role for hyper IgD in the pathogenesis of HPF [32]. Nevertheless, the upstream factors for hyper IgD in HPF remain unidentified. We would surmise that an elucidation of this mechanism might give us indications of how very different mutations are able to converge to produce a relatively

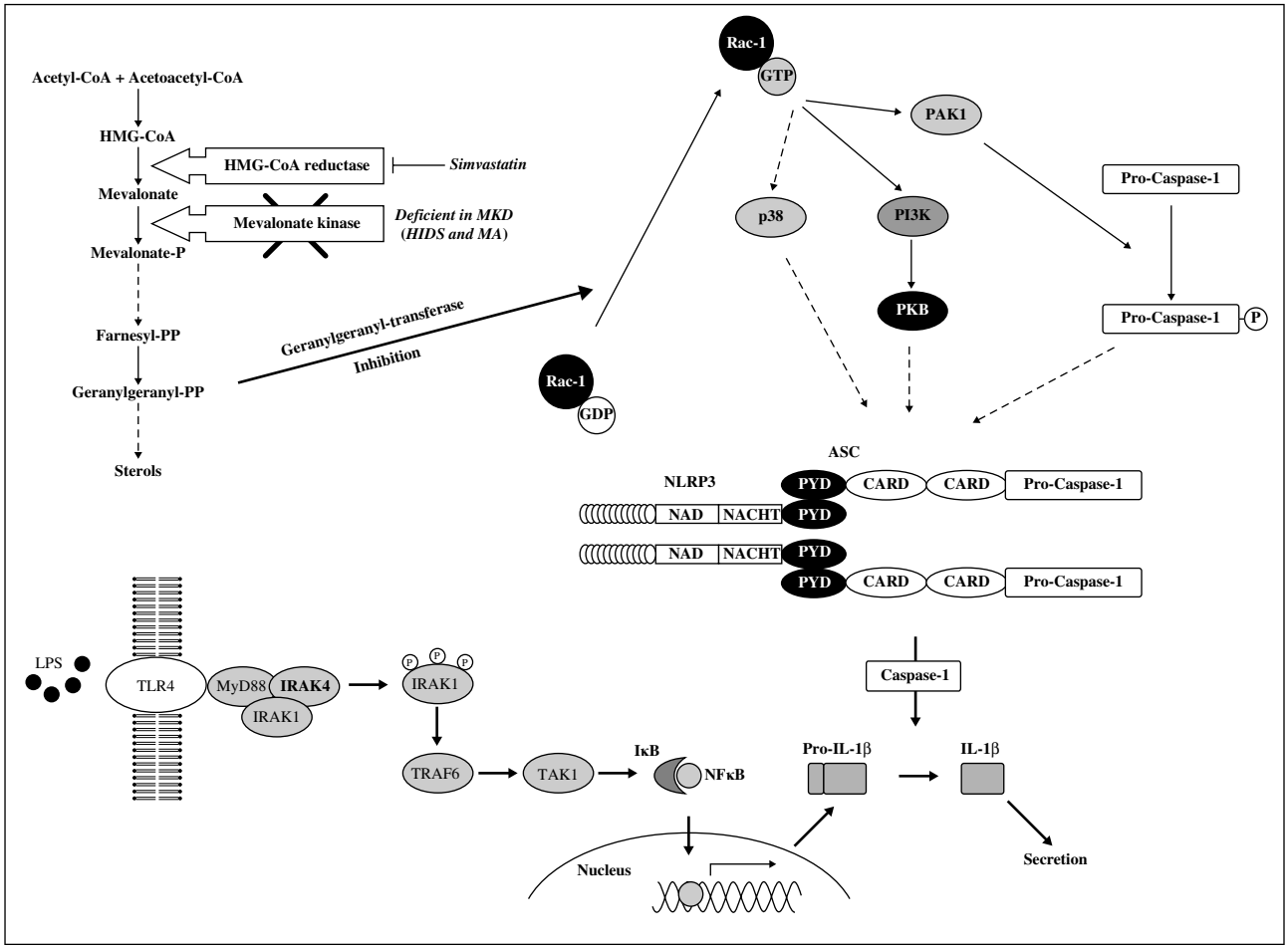

Figure 1

Hypothetic molecular events from the inhibition of the mevalonate pathway to caspase-1 activation and IL-1β release.
HMG-CoA: 3-hydroxy-3-methylglutaryl Co-enzyme A; MKD: mevalonate kinase defiency; HIDS: hyperimmunoglobulinemia D, periodic fever syndrome; MA: mevalonic aciduria; PP: pyrophosphate; PAK1: protein-associated kinase1; PKB: protein kinase B; PI3K: phosphoinositide 3-Kinase; MyD88: myeloid differentiation primary response gene 88; TLR4: Toll-like receptor 4; IRAK: interleukin-1 receptor-associated kinase; TRAF6: TNF receptor-associated factor 6; TAK1: TGF-β-activated kinase 1; NFκB: nuclear factor κB.
NLRP3 inflammasome is a multiprotein complex containing the proteins NLRP3/cryopyrin ASC (apoptosis-associated speck-like protein containing a CARD) and pro-caspase-1. The oligomerisation of the inflammasome leads to IL-1β processing and release through caspase-1 activation. NALP: NACHT-LRR-PYD-containing protein; LRR: leucine-rich repeats; PYD: pyrin domain; NAD: NALP-associated domain; CARD: caspase recruitment domain.

close group of diseases characterized by recurrent attacks of fever and localized organ inflammation.

During attacks, the marked inflammatory syndrome is associated with increased serum levels of IL-1, IL-6 and interferon (IFN)-γ, as well TNF receptors [33], with a strong *in vitro* production of IL-1β [34], IL-6 and TNF-α by peripheral blood mononuclear cells (PBMCs) [33, 35], spontaneously and even more after cell stimulation. As expected, these culture supernatants induced acute phase protein production [35].

ANIMAL MODELS OF MKD

In mice, the deletion of the genes encoding either HMG-CoA reductase (Hmgcr-/-), squalene synthase (SS-/-) or MK (*Mvk*-/-), three enzymes belonging to the cholesterol biosynthesis pathway, result in embryonic lethality [36-38]. However, a single report has shown that the deletion of one *Mvk* allele in C57Bl6 mice increased significantly the serum levels of IgD, IgA and TNF-α compared to control mice [36]. On another hand, it has been suggested that the administration to BALB/c mice of aminobisphosphonate alendronate, a drug inhibiting FPP synthase, provides a model for typical MKD inflammatory episodes [39]. This inflammation was reduced after treatment with exogenous isoprenoid intermediates, suggesting the important role of isoprenoids in MKD inflammation.

STATINS AS INHIBITORS OF THE MEVALONATE PATHWAY: PHARMACOLOGICAL TOOLS TO MIMIC MKD?

Taking advantage of the fact that statins are potent inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) (the enzyme directly upstream of MK), recent studies have used this pharmacological tool to help unravel the molecular mechanisms linking MKD to inflammation. Statins impair cholesterol synthesis by inhibiting the rate-limiting step in the mevalonate pathway by preventing the reduction of HMG-CoA to mevalonate, resulting in a

Table 1
Hereditary periodic fever syndrome

	FMF	MKD (HIDS and MA)	CAPS (FCAS, MWS, NOMID and CINCA)	TRAPS
Mode of inheritance	Recessive	Recessive	Dominant	Dominant
Age at onset (years)	< 20	Child (median 6 month old)	Infancy-1st 6 months	Childhood, adolescence
Duration attack (day)	1-4	3-7	Variable	1 to 3 weeks
Abdominal pain	Very frequent (serosa)	Frequent	Rare	Frequent (serositis, abcess)
Thoracic pain	Unilateral pleurisy	Unusual	Rare	Unilateral pleurisy
Skin	Erysipeloid eythema (rare < 5%)	Maculo-papular/nodular rash	Urticuria/erythema	Erysipeloid erythema including upper limbs/ various rashes
Musculoskeletal	Monoarthritis	Polyarthralgia	From arthalgias to destructive arthropathy	Arthralgia/arthritis
Eye	Rare: conjunctivitis	Conjunctivitis, uveitis*, cataract*	Conjunctivitis, papil oedema	Conjunctivitis, orbital edema
Amyloidosis	60-75%	Rare	25%	25%
IgD sera levels	++	+++	++	+
Chromosome site	16p13.3	12q24	1q44	12p13
Mutated gene	*MEFV*	*MKV*	*CIAS1*	TNFRSF1A
Gene product	Pyrin/marenostrin	Mevalonate kinase	Cryopyrin/NALP3	TNF receptor type 1A
NALP3 inflammasome	Regulator (?)	?	Belong to the complex	?
Caspase-1 activation	Yes	Yes	Yes	?
Treatment	Colchicine; IL-1 inhibitor?	Steroids, TNF inhibitor?, IL-1 inhibitor?	IL-1 inhibitor	Steroids, TNF inhibitor, IL-1 inhibitor

* Features exclusively seen in MA.
FMF: familial mediterranean fever; MKD: mevalonate kinase deficiency; HIDS: hyper-IgD and periodic fever syndrome; MA: mevalonic aciduria; CAPS: cryopyrin-associated periodic syndromes; MWS: Muckle-Wells syndrome; NOMID: neonatal-onset multisystem inflammatory disease; CINCA: chronic infantile neurologic cutaneous articular syndrome; TRAPS: TNF (tumor necrosis factor) receptor associated periodic syndrome; TNFRSF1A: TNF receptor superfamily 1A.

decrease in non-sterol isoprenoids downstream of mevalonate. Statins are extensively prescribed for the prophylactic treatment of cardiovascular events [40-43]. Besides reducing cholesterol serum levels, statins have numerous immunomodulatory effects. *In vitro*, it is recognized that statins specifically enhance the production of IL-1β and IL-18 by LPS-activated human PBMCs, as well as purified and THP-1 monocytes, and the WEHI265.1 murine cell line [34, 44-46]. This is mediated by lipophilic statins (atorvastatin, lovastatin and simvastatin), whereas the hydrophilic pravastatin had no effect [44]. IL-1α release is also enhanced by LPS-activated human PBMCs and THP-1 cells [46]. Results are more controversial for other proinflammatory cytokines derived from monocytes. Kiener *et al.* have reported that simvastatin also enhances TNF-α and IL-8 [44] secretion, whereas others have shown that statins are ineffective or indeed inhibit TNF-α, IL-6 or IL-8 expression and secretion by LPS-stimulated monocytes [45-47]. Production of the immunosuppressive cytokine IL-10 by activated monocytes is also inhibited by simvastatin *in vitro* [46]. Regarding T lymphocyte-derived cytokines, statins inhibit the release of IFN-γ, IL-2, IL-10 and IL-4 by antiCD3/PMA stimulated-PBMCs cells, but have no effect on the production of cytokines of the IL-1 family [46]. In contrast, the atypical anti-CD2/anti-CD28 stimulation of PBMCs increases IL-1β production in the presence of statins [48]. *In vivo*, statins have complex immunosuppressive properties that operate independently of lipid lowering [49]. IL-1β production by LPS-activated whole peripheral blood [50] or monocytes [51] from statin-treated patients with hypercholesterolemia is unchanged or decreased, and is associated with a decrease in TNF-α and IL-6 production. These results suggest that *in vivo*, the inhibitory effect of statins on cytokine synthesis is very effective in suppressing the IL-1 synthesis observed *in vitro*.

Interestingly, if simvastatin specifically enhances IL-1β release by monocytes, it is worth noting that pro-IL-1β expression is not modified [45, 46]. Simvastatin has been shown to enhance caspase-1 activity, this being the enzyme responsible for IL-1β and IL-18 maturation, and also indirectly involved in IL-1α processing.

The non-sterol isoprenoids geranylgeranyl-pyrophosphate (GGPP) [34] and farnesyl-pyrophosphate (FPP) [1, 23, 52], metabolites synthesized downstream of MK are suspected of playing a crucial role in MKD. Frenkel *et al.* have further demonstrated that shortage of isoprenoid end products contributes to increased IL-1β secretion by MK-deficient PBMCs [48]. FPP and GGPP are precursors for the isoprenylation of small G proteins [53], an enzymatic process necessary for their localization at the plasma membrane, and allowing their signal transduction activity. FPP allows farnesylation of Ras-family proteins, while most Rho-family proteins are geranylgeranylated. The inhibition of the mevalonate pathway with a geranylgeranyl-transferase inhibitor, as well as simvastatin, leads to a caspase-1-dependent release of IL-1β and IL-18 by THP1-activated cells [45, 46] and LPS-activated PBMCs, whereas farnesyl transferase inhibitors have no effect [46]. Geranylgeranylation is associated with the activity of Rac-1, a small G-protein of the Rho family reported to play a critical role in caspase-1 activation [34, 52]. Two independent studies have reported that Rac-1 could be implicated in this process

[46, 54]. Under simvastatin treatment, Rac-1 was partially dissociated from the plasma membrane to the cytoplasm, and the level of GTP-bound, active form of Rac-1 was found to be increased. The p21-activated kinase1 (PAK1) could be a link, since its activation by Rac-1 leads to caspase-1 phosphorylation, required for its activity [55]. PI3K and protein kinase B (PKB)/c-akt have also been suggested to be a link between Rac-1 and caspase-1 activation [54]. In any event, inhibition of Rac-1 in PBMCs from MKD patients results in a decrease of IL-1β release [54]. The molecular relationship between the increased GTP-bound form of Rac-1 and caspase-1 activation remains to be fully explained. Caspase-1 requires inflammasome oligomerisation to become active. We discussed earlier the key role of NLRP3 inflammasome activation in FMF and CAPS; it remains an open question as to whether NLRP3 is a molecular link between Rac-1 and caspase-1.

In order to compare the previous pharmacological model to the genetic inhibition of the mevalonate pathway, we further studied IL-1β and IL-6 secretion by activated dermal fibroblasts from healthy donors and MKD patients, in the presence or absence of simvastatin.

While IL-6 production was unchanged, IL-1β secretion by activated fibroblasts from MKD patients was increased when compared to the secretion from those of control donors. In the absence of activation, IL-1β is not detected in fibroblast supernatants. The secretion of IL-1β by simvastatin-treated fibroblasts from healthy donors is increased, as is the IL-1β secretion by untreated fibroblasts from MKD patients. On the other hand, simvastatin had no effect on IL-1β secretion by fibroblasts from MKD patients *(figure 2)*. We conclude that both pharmacological (simvastatin) and genetic (MKD) inhibition of the mevalonate pathway lead to an increase in IL-1β production by fibroblasts, suggesting the involvement of similar molecular mechanisms and reinforcing the idea that using statins on activated monocytes is a model relevant for mimicking MKD *in vitro*.

CONCLUSION

In contrast to the majority of HPFs, for which a direct link between genetic mutations and inflammation has been demonstrated and mainly involving disorders in the secretion and/or signalling of pro-inflammatory cytokines, the molecular mechanisms linking MKD to inflammation remained to be fully elucidated. Many years ago it was suggested that cytokines play a crucial role in the recurrent inflammation of HIDS [33]. This is now known to be the case for any inflammatory disease, irrespective of their precise role in the physiopathology. Likewise, a role for cholesterol pathway intermediates and protein isoprenylation in the pathogenic inflammatory response of HIDS has also been suspected [1]. Taking advantage of statins and there ability to mimic MKD *in vitro*, independent studies have demonstrated that the inhibition of the mevalonate pathway specifically activates caspase-1 by a mechanism involving Rac-1, resulting in a dramatic and specific increase in IL-1α, IL-1β and IL-18 release [45, 46, 54]. This approach has revealed a cytokine "signature" focused on specific IL-1 production by monocytes, whereas the production of inflammatory cytokines, including IL-1, by T cells appears unchanged. *A posteriori*, the activation of caspase-1 in the context of HPF is not a surprise since an over-activation of inflammasome/caspase-1 is well known in FMF and CAPS [16, 17]. However, if direct links between mutated pyrin and cryopyrin, and the inflammasome have been demonstrated in FMF and CAPS, the molecular mechanisms linking Rac-1 to the inflammasome remain to be further investigated and clarified. It is also interesting to note that *a priori* heterogeneous mutations all converge to the dysregulation of the inflammasome assembly, leading to a group of fairly homogeneous, recurrent diseases. The spectacular reduction of febrile attacks in severe HIDS patients under IL-1ra (anakinra) treatment [56, 57], as previously reported for the treatment of CAPS [58, 59], is in accordance with the key role of IL-1 in the pathophysiology of

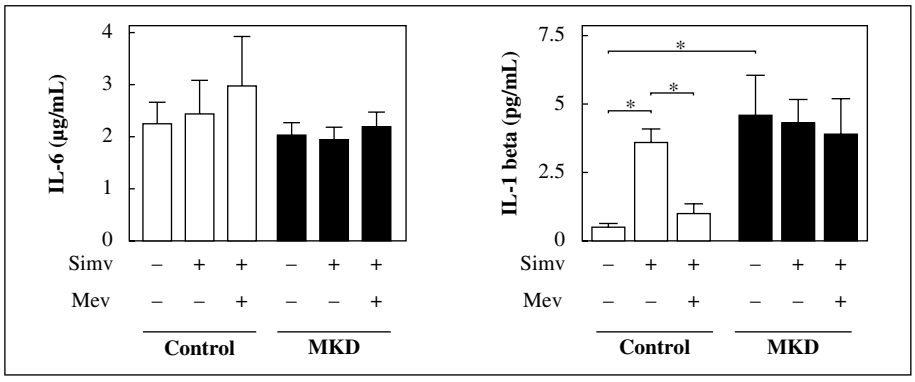

Figure 2

IL-6 and IL-1β secretion by dermal fibroblast from healthy donors and patients with MKD. Dermal fibroblasts were obtained by explant culture of human skin from patients with MKD or from control donors as previously described [63]. They were seeded at 10 000 cells per cm^2 in 6-well plates in DMEM supplemented with Glutamax-I, 10% heat-inactivated fetal calf serum and antibiotics. At 80% confluence, fibroblasts from healthy donors (open bars) or MKD patients (filled bars) were activated with 10 ng/mL IL-1α and 10 ng/mL TNF-α for 24 hours and cultured with or without 10 µM simvastatin, and 100 µM mevalonate for an additional 24 hours. Supernatants were collected, and IL-6 (**A**) and IL-1β (**B**) were assayed by high sensitivity ELISA (0.5 pg/mL) as previously described [46]. Each bar represents mean ± SEM (n = 4 for control and n = 5 for MKD). * $p < 0.05$ based on one-way ANOVA followed by the Newman-Keuls test.

MKD [34, 45, 46]. Finally, the very recent reports of a new, severe, autoinflammatory disease associated with a deficiency in IL-1ra (DIRA), and the complete resolution of all symptoms with anakinra treatment, further demonstrates the primary role of the balance IL-1/IL-1ra in autoinflammatory diseases [60-62]. Nonetheless, some patients with HPF do not respond to anakinra therapy, and it is an open question as to the reason why [57]. Even if we are dealing with a single cytokine disorder at the origin, a complex cytokine network is induced *in vivo* as a function of the pharmacokinetic properties of IL-1ra, including amplification loops, synergy, and implementation of a vicious circle, differing between individuals. Further knowledge of the physiological control of HPF inflammation might help us to understand the variability of response to treatment, and thus to the design of new, more effective therapies.

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