REVIEW ARTICLE

Metabolic interactions between eicosanoids in blood and vascular cells

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Introduction

Eicosanoids (or icosanoids) are chemical compounds including C_{20} polyunsaturated fatty acids and their numerous oxygenated metabolites, the most common being arachidonic acid (5,8,11,14-eicosatetraenoic acid) and its derivatives. Three main pathways lead to these products from the fatty acid substrate. They are (i) the cyclo-oxygenase system, producing prostanoids, which include non-prostanoid derivatives like thromboxanes in addition to true prostaglandins (Samuelsson *et al.*, 1978; Smith, 1980; Moncada, 1982), (ii) various lipoxygenase products (Needleman *et al.*, 1986), and (iii) NADPH-dependent cytochrome *P*-450 epoxigenase metabolites (Capdevila *et al.*, 1982, 1988; Snyder *et al.*, 1983). Fig. 1 summarizes the main oxygenase pathways occurring in arachidonic acid metabolism. Although arachidonic acid is the main polyunsaturated fatty acid in blood and vascular cells, other eicosanoid precursors may arise under certain nutritional states, then providing other prostanoids and/or lipoxygenase products (Willis, 1981; Goodnight *et al.*, 1982; Dyerberg, 1986). In addition, octadecanoids and docosanoids, deriving from C_{18} and C_{22} polyunsaturated fatty acids, respectively, may also occur during cell activation (Salem *et al.*, 1986; Lagarde, 1988).

In recent years, cell–cell interactions via eicosanoids as well as interactions between eicosanoids themselves have been more and more accounted for. This review will focus on these aspects and will include: (i) the further metabolism by an acceptor cell of one eicosanoid produced by a donor cell, (ii) the modulation of arachidonic acid metabolism by various eicosanoids formed either in the same type of cell or another one (acceptor cell), and (iii) interactions between fatty acid precursors of eicosanoids.

Oxygenated eicosanoids as biochemical precursors

This topic concerns the metabolism of one eicosanoid by an acceptor cell after being produced by a donor cell, and could be called a cell-to-cell donation system. This will be restricted to transfers between cells of different types. Since eicosanoids are lipophilic substances, and are believed to be capable of easily crossing plasma membranes, the donation of one eicosanoid produced by one cell to the same cell type will not be considered.

In most cases, the eicosanoid transferred to another cell type for further metabolism is an oxygenated derivative of arachidonic acid. One of the first reports relating

to this was the metabolism of prostacyclin (PGI_2) and/or of its stable metabolite, 6-oxo- $PGF_{1\alpha}$, into 6-oxo- PGE_1 by platelets (Wong, *et al.*, 1980b), prostacyclin being not formed in platelets themselves but originating mainly from vascular endothelial cells. The process is catalysed by NAD^+ -dependent 9-prostaglandin dehydrogenase as described in hepatocytes (Wong *et al.*, 1980a). The biological interest of such a transformation is to provide a prostanoid, 6-oxo- PGE_1 , which is much more stable than PGI_2 and which however shares its biological activity. Although not derived from further metabolism by blood or vascular cells, the specific reduction of PGD_2 by the liver into $9\alpha,11\beta$ - PGF_2 has to be mentioned. This stereospecific reduction is catalysed by 11-prostaglandin dehydrogenase and seems to be restricted to human liver (Liston & Roberts, 1985), whereas the liver from other species may also produce true $PGF_{2\alpha}$ or $9\alpha,11\alpha$ - PGF_2 (Wong, 1981; Reingold *et al.*, 1981; Watanabe *et al.*, 1981). The conversion of PGD_2 into $9\alpha,11\beta$ - PGF_2 may be then of pathophysiological relevance since the product increases blood pressure when present in the circulation (Liston & Roberts, 1985). Several other reports concern PGI_2 production from cyclic prostaglandin endoperoxide, PGH_2 , of platelet origin. The first such report, from Marcus *et al.* (1980), referred to the contribution of stimulated platelets in providing endoperoxides as substrates for the vascular endothelial prostacyclin synthase. At the opposite, a reciprocal transfer of endothelial endoperoxides for utilization by thromboxane synthase does not seem to occur (Schafer *et al.*, 1984). The unidirectional transfer is concerned in the pathophysiological model of atherosclerosis where an increase of urinary prostacyclin metabolites could be observed (Fitzgerald *et al.*, 1984). Such an increase has been attributed to platelet hyperfunctions *in vivo*, and is characterized by PGH_2 hyperproduction. This relates to 'basal' production of PGH_2 and it is of interest, in this respect, that PGH_2 transfer from platelets to cultured endothelial cells appears more efficient under 'basal' conditions than under thrombin stimulation (Bordet & Lagarde, 1988). Finally, another report has described the transfer of PGH_2 from platelets to de-endothelialized rabbit aorta to yield PGI_2 (Papp *et al.*, 1986), confirming the positive co-operation between platelets and the vascular wall for prostacyclin formation. In addition, leukocytes could also contribute to prostacyclin production, presumably from PGH_2 of platelet origin. This has been suspected to explain the presence of prostacyclin in serum and was believed to be

Abbreviations used: PG, prostaglandin; LT, leukotriene; HETE, hydroxyeicosatetraenoic acid; diHETE or triHETE, di- or trihydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; PAF, platelet-activating factor; TX, thromboxane.

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Fig. 1. Main oxygenation pathways of arachidonic acid

due to monocytes as the source of prostacyclin synthase (Defreyn *et al.*, 1982). A recent report confirmed the involvement of platelets in such a formation via lymphocytes (Wu *et al.*, 1987). Although the latter cells are devoid of oxygenase activities (Goldyne & Stobo, 1982; Goldyne *et al.*, 1984), their contribution might then be of interest to the prostacyclin homeostasis of circulating blood.

Other recent reports concern the platelet lipoxygenase endproduct of arachidonic acid, 12-hydroxyeicosatetraenoic acid (12-HETE). Although its biological activity outside platelets is not entirely defined, it seems to be involved in enhancement of epidermal cell proliferation (Chan *et al.*, 1985), chemotaxis for neutrophils (Turner *et al.*, 1975; Goetzl *et al.*, 1980), chemokinesis for smooth muscle cells (Nakao *et al.*, 1982), and potentiation of mononuclear pro-coagulant activity (Lorenzet *et al.*, 1986). Its further metabolism by blood and vascular cells other than platelets may be then considered as a regulating process of such activities. Simultaneously and independently, Borgeat *et al.* (1982) and Marcus *et al.* (1982) described the formation of (5*S*,12*S*)-dihydroxy-6,10-*trans*-8,14-*cis*-eicosatetraenoic acid [(5*S*,12*S*)-diHETE] when neutrophils are incubated with (12*S*)-HETE or platelets with (5*S*)-HETE. The dihydroxylated fatty acid has been identified as a double lipoxygenase product and renamed leukotriene B_x (LTB_x), as a stereo- and geometric isomer of LTB₄ or (5*S*,12*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid. These findings do not contradict fundamentally a previous paper reporting the formation of LTB_x in leukocytes, such cells being likely to be contaminated by platelets (Lindgren *et al.*, 1981). It is assumed that LTB_x formation from 12-HETE predominates over that from 5-HETE, accounting for the quantitative importance of 12-HETE formation in platelets as compared with leukocytes where 5-HPETE is preferentially transformed into leukotrienes rather than into 5-HETE. On the other hand, the high ratio platelets/leukocytes also favours this assumption. As for the production of LTB₄, that of LTB_x requires activated leukocytes, the 5-lipoxygenase being a calcium-dependent enzyme (Jakschik & Lee, 1980). More recently, the ω -hydroxylation of 12-HETE in unstimulated neutrophils has been described (Marcus *et al.*, 1984) and further characterized as 12(*S*),20-diHETE, a product of a cytochrome *P*-450 mono-oxygenase-dependent process (Marcus *et al.*, 1987). This ω -hydroxylation may also occur on LTB_x to provide (5*S*),12(*S*),20-triHETE (Lindgren *et al.*, 1981; Marcus *et al.*, 1988). Recent investigations in our laboratory have allowed us to determine the substrate specificity of leukocyte ω -hydroxylase towards monohydroxylated fatty acids produced by platelets. This revealed that various 12-hydroxyeicosapolyenoic acids are equal substrates of the leukocyte enzyme but that (12*S*)-hydroxy-5,8,10-heptadecatrienoic acid (HHT), the monohydroxylated byproduct of cyclooxygenase activity, was virtually not ω -oxidized. This agrees with a similar quasi-absence of ω -hydroxylated 15-HETE, and leads to suggest that the position of the hydroxyl group, closer to the ω end in the latter two compounds, might be crucial for enzyme activity (Guichardant & Lagarde, 1988).

Although transformation of the precursor is not due to an acceptor cell, the example of specific metabolism of 12- and 5-HPETE by blood plasma haemoproteins must be stated. It has been shown that incubating 12-HPETE

with haematin or haemoglobin provokes its specific rearrangement into hydroxyepoxy derivatives, 8-hydroxy- and 10-hydroxy-11,12-epoxyeicosatrienoic acids (Pace-Asciak, 1984*a,b*). Similarly, but with a different mechanism, 5-HPETE is isomerized into leukotriene A₄ (LTA₄) by haemoglobin (Radmark *et al.*, 1984). The physiological relevance of such isomerization is however questionable since hydroperoxide precursors are likely to be trapped very efficiently in the corresponding donor cell, e.g. by the glutathione-dependent peroxidase associated with the lipoxygenase pathway in platelets (Bryant *et al.*, 1982) and by both a similar peroxidase and by leukotriene synthase activities in leukocytes (Needleman *et al.*, 1986).

The most recent findings relating to eicosanoid further metabolism by other cell types concern leukotrienes and especially LTA₄ (5,6-epoxy-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid). This epoxy derivative of arachidonic acid is a pivotal precursor in the biosynthesis of other leukotrienes (Borgeat & Samuelsson, 1979). This labile compound (Fitzpatrick *et al.*, 1982) can be very efficiently transformed into LTB₄ by human erythrocytes which possess a cytosolic epoxide hydrolase (Fitzpatrick *et al.*, 1984; McGee & Fitzpatrick, 1986). In addition to lymphocytes, erythrocytes represent another example of cells virtually devoid of dioxygenase activity (Schrier, 1967; Kobayashi & Levine, 1983), which are however able to generate lipid mediators through cell-cell interactions. Further metabolism of LTA₄ into peptidoleukotriene, LTC₄ [(5*S*)-hydroxy-(6*R*)-*S*-glutathionyl-7,9,11,14-eicosatetraenoic acid], by vascular endothelium, which is unable to produce LTA₄ itself (Gorman *et al.*, 1985; Miller *et al.*, 1985), has been described (Feinmark & Cannon, 1986). Similar conversion has been observed in platelets, which also fail to synthesize LTA₄ (Maclouf & Murphy, 1988). In both cell populations, the ability to produce LTC₄ appears quite substantial, making the process of physiological relevance. The potentiation of adrenaline-induced platelet aggregation by LTC₄ (Mehta *et al.*, 1986) reinforces the biological interest of the platelet contribution to LTC₄ formation from LTA₄ of leukocyte origin. Vascular smooth muscle cells have also been recently reported to be able to convert LTA₄ from other cellular origins into LTC₄ (Feinmark & Cannon, 1987). This may be particularly important considering that such a transcellular LTA₄ metabolism leads to the generation of the vasoconstricting agent LTC₄ (Drazen *et al.*, 1980; Greenwald *et al.*, 1984) in the proper target tissue. Finally, the vascular wall (Piper & Galton, 1984) as well as macrophages (Nagoka & Yamashita, 1987), having the capacity to convert LTC₄ into LTD₄ and LTE₄, could contribute to producing LTD₄ and LTE₄ from LTC₄ and LTD₄ derived from neutrophils. The overall cell-cell interactions via these processes are summarized in Fig. 2.

Modulation of arachidonic acid metabolism by eicosanoids

This part of the review will concern various eicosanoids of which the synthesis is modified by other eicosanoids not convertible into the former. This modulation may concern the same cell types as well as neighbouring cells of different populations.

Numerous papers have described the biological effect of prostanoids and the reader can refer to the reviews from Samuelsson *et al.* (1978) and Needleman *et al.*

Fig. 2. Some examples of interaction between blood and vascular cells via eicosanoids transformed in the acceptor cell

Further abbreviation: AA, arachidonic acid.

(1986). In the context of the present review, it may however be useful to restate a common mechanism of several prostaglandins like PGD_2 , PGE_2 and PGI_2 in altering cell cyclic AMP via adenylate cyclase stimulation, and subsequently modulating arachidonic acid release at the phospholipase A_2 level, depending on the target cell. This has been well documented in human platelets where PGD_2 and PGI_2 stimulate adenylate cyclase (Mills & MacFarlane, 1974; Gorman *et al.*, 1977), although these prostaglandins have different receptor sites (Schafer *et al.*, 1979). Cyclic AMP being a potent inhibitor of platelet liberation of endogenous arachidonic acid (Lapetina *et al.*, 1977; Minkes *et al.*, 1977), PGD_2 and PGI_2 will inhibit eicosanoid synthesis in platelets. The physiological relevance of such an inhibition by PGD_2 is reinforced in considering that this prostaglandin is the main cyclooxygenase product of human mast cells (Lewis *et al.*, 1982). PGI_2 has also been reported to inhibit its own formation in vascular endothelial cells with a similar mechanism (Brotherton & Hoak, 1982), but this was controversial (Brotherton *et al.*, 1982). Finally, as PGE_2 exhibits a biphasic effect on platelet adenylate cyclase activity [an inhibition at low concentrations (below 5×10^{-7} M) and an activation at higher concentrations (Salzman *et al.*, 1972; Malmsten *et al.*, 1976)], it would act accordingly on the liberation of endogenous arachidonic acid, although the facilitation of such a liberation by decreasing platelet cyclic AMP is not proved.

In addition to the effect of prostaglandins, that of lipoxygenase products has been more recently investigated and seems particularly promising. First it has been shown that 15-HETE, the end-product of the 15-lipoxygenation of arachidonic acid, is an inhibitor of leukotriene synthesis in polymorphonuclear leukocytes, acting

at the 5-lipoxygenase step (Vanderhoek *et al.*, 1980a). The potency of 15-HETE towards 12-lipoxygenase is however 10-fold higher than towards 5-lipoxygenase. The effect on 12-lipoxygenase is shared by some other 15-lipoxygenase products, the potential of inhibition being increased with the number of *cis* double bonds of the inhibitors (Mitchell *et al.*, 1984). The inhibitory effect of 15-HETE on 5-lipoxygenase might depend on the target cell, since an opposite effect has been observed in a mast/basophil cell line and interpreted as a direct activation of a cryptic 5-lipoxygenase (Vanderhoek *et al.*, 1982). Another example of stimulation has been given in human neutrophils, where both 5-HETE and LTB_4 potentiate their own formation as well as that of platelet-activating factor (PAF), the concomitant product of the stimulated cells (Ramesha & Pickett, 1986). It has been concluded in this case that 5-HETE and LTB_4 may enhance the expression of phospholipase A_2 (Billah *et al.*, 1985), as reported previously in stimulated HL-60 granulocytes (Siegel *et al.*, 1982). This contrasts with data obtained with normal platelets and neutrophils showing the inhibition of cell phospholipase A_2 activity by 5-, 12- or 15-HETE (Chang *et al.*, 1985). The physiological relevance of the latter data is however difficult to evaluate, since the IC_{50} observed for HETEs reached 5×10^{-5} M.

As compared with the corresponding HETEs, the inhibitory effect of hydroperoxy derivatives is usually higher. As an example, 12- and 15-HPETE have been compared with 12- and 15-HETE on arachidonic acid-derived eicosanoid production in macrophages (Humes *et al.*, 1986). Hydroperoxy derivatives appear as irreversible inhibitors of both cyclooxygenase (PGE_2 production) and lipoxygenase (LTC_4 production), whereas the corresponding hydroxylated compounds exhibit re-

versible effects. This could be explained by destructive effects of hydroperoxides on oxygenases, at least at relatively high doses (Siegel *et al.*, 1979a). The destruction has been assumed to be due to oxygen radicals generated from hydroperoxides, and has been well documented with cyclo-oxygenase as the target (Ham *et al.*, 1979; Kuehl & Egan, 1980; Egan *et al.*, 1981). This concept has to be taken with caution, since low concentrations of hydroperoxides oppositely enhance cell oxygenase activities (Hemler *et al.*, 1978; Lands, 1984). This is illustrated by platelet 12-lipoxygenase which is stimulated by its hydroperoxide product, 12-HPETE (Siegel *et al.*, 1979b). Similarly, 12-HPETE stimulates leukocyte 5-lipoxygenase product formation, LTB₄ in neutrophils (Maclouf *et al.*, 1982) and LTC₄ in monocytes (Maclouf *et al.*, 1985). It may be however suspected that the potentiating effect of 12-HPETE is more likely to occur in the mother cell instead of another cell type, since normal platelets, from which it originates, convert it efficiently to 12-HETE via the glutathione peroxidase associated with 12-lipoxygenase. The pathophysiological relevance of the paracrine effect of 12-HPETE cannot be however excluded in some platelets of depressed antioxidant status, as in aging (Vatassery *et al.*, 1983; Vericel *et al.*, 1988) and diabetes (Watanabe *et al.*, 1984). In addition, the stimulating effect of hydroperoxides might be crucial for eicosanoid formation from other precursors than arachidonic acid, and will be reviewed in the next paragraph.

Some cytokine effects of leukotrienes and lipoxins have also been reported on the oxygenated metabolism of arachidonic acid. This has been first reported in macrophages where LTC₄ stimulates prostaglandin release (Feuerstein *et al.*, 1981), and it has since been well documented with endothelial cells as the target. In cultured human endothelial cells, LTC₄ stimulates prostacyclin synthesis (Benjamin *et al.*, 1983; Cramer *et al.*, 1983). This stimulation seems to depend on LTC₄-specific receptors on the cell, suggesting it is subsequent to phospholipase A₂ activation. As a matter of fact, McIntyre *et al.* (1986) have found that LTC₄-stimulated endothelial cells synthesize PAF concomitantly, as a co-product of phospholipase A₂ activation. Since LTC₄ is produced in endothelium from LTA₄ of leukocyte origin (Feinmark & Cannon, 1986), we may consider that leukocyte adherence to the vessel wall might be coupled with prostacyclin formation in the endothelium. Finally, a recent report has described the potentiation of thromboxane formation in human polymorphonuclear leukocytes by lipoxin A [(5S,6R,15S)-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid] (Conti *et al.*, 1987) a newly discovered leukocyte double lipoxygenation (15-then 5-lipoxygenase) product of arachidonic acid (Serhan *et al.*, 1984).

Although not belonging to the eicosanoids, the 13-hydroxy derivative of linoleic acid must be accounted for in the context of this review. (13S)-Hydroxy-9-*cis*-11-*trans*-octadecadienoic acid ('13-HODE') is synthesized by endothelial cells (Buchanan *et al.*, 1985) and leukocytes (Claeys *et al.*, 1985; Soberman *et al.*, 1985). Recent reports have shown that this 'octadecanoid' may inhibit the formation of 5-lipoxygenase products in leukocytes (Camp & Fincham, 1985), may stimulate prostacyclin synthesis in endothelial cells (Setty *et al.*, 1987a), and may depress thromboxane and enhance 12-HETE formation in platelets (Setty *et al.*, 1987b). The mechanisms of

these different effects are unknown, except for the stimulation of prostacyclin synthesis which seems to be related to endothelial phospholipase A₂ activation.

Interactions between fatty acid precursors

This section concerns both the antagonism and synergism between various fatty acids which may be potential substrates of cyclo-oxygenase and/or lipoxygenases. Apart from arachidonic and linoleic acids, most of the other polyunsaturated fatty acids, which may be substrates of dioxygenases, are solely of nutritional value in blood and vascular cells and previous reviews can be referred to for their biological interest (Willis, 1981; Goodnight *et al.*, 1982; Dyerberg, 1986). The present review will be restricted to some points relevant to biochemical interactions between these fatty acids.

Data concerning cyclo-oxygenase activity have been mostly known for several years, at least for the three classical substrates, dihomo- γ -linolenic acid (8,11,14-eicosatrienoic), arachidonic acid (5,8,11,14-eicosatetraenoic) and timnodonic acid (5,8,11,14,17-eicosapentaenoic), the precursors of the monoene, diene and triene prostanoids, respectively (Needleman *et al.*, 1976). The interaction can be summarized by the inhibition of arachidonic acid cyclo-oxygenation by dihomo- γ -linolenic acid (Kernoff *et al.*, 1977), and by timnodonic acid (Needleman *et al.*, 1979), in a competitive way. More recently, two docosapolyenoic acids have been recognized as additional substrates of cyclo-oxygenase. They are adrenic acid (7,10,13,16-docosatetraenoic) and 4,7,10,13,16-docosapentaenoic acid. The former has been described as the precursor of dihomo-PGI₂ in endothelial cells (Campbell *et al.*, 1985) and of dihomothromboxane in platelets (Van Rollins *et al.*, 1985), and the latter as the precursor of Δ^4 -dihomo-prostanoids (Milks & Sprecher, 1985). These studies showed that adrenic acid appears as a potent inhibitor of arachidonic acid cyclo-oxygenation, presumably via a competitive process. A competitive inhibition of LTB₄ formation by timnodonic acid has also been recently observed (Lee *et al.*, 1984).

A number of C₁₈, C₂₀ and C₂₂ polyunsaturated fatty acids are potential substrates of blood and vascular cell lipoxygenases, then providing a cohort of octadecanoids, eicosanoids and docosanoids, respectively. The biochemical regulation of their synthesis has not been yet fully investigated, but such a regulation can be proposed, essentially in platelets and endothelium. Like the lipoxygenation of arachidonic acid, which is potentiated by its own product, 12-HPETE (Siegel *et al.*, 1979b), that of some other fatty acid substrates is highly sensitive to the peroxide status of the cell, in relation to the oxygenation of arachidonic acid. As a matter of fact, both the platelet cyclo-oxygenation and lipoxygenation of dihomo- γ -linolenic and timnodonic acids are markedly potentiated by arachidonic acid (Boukhache & Lagarde, 1982), apparently through 12-HPETE (Morita *et al.*, 1983; Croset & Lagarde, 1985). This agrees with the requirement of a certain peroxide status for the oxygenation of some polyunsaturated fatty acids, of which timnodonic acid has been mostly studied (Lands, 1984). In blood and vascular cells, arachidonic acid appears as the physiological potentiator in providing specific peroxides. Amongst various polyunsaturated fatty acids, timnodonic acid seems to be entirely dependent on such peroxides, whereas the dependence of others is weaker. As

Fig. 3. Some metabolic interactions between fatty acid precursors of oxygenated derivatives

Abbreviations: 20:4n-6, 5,8,11,14-eicosatetraenoic acid (arachidonic acid); 20:3n-6, 8,11,14-eicosatrienoic acid; 20:5n-3, 5,8,11,14,17-eicosapentaenoic acid; 22:4n-6, 7,10,13,16-docosatetraenoic acid; 22:6n-3, 4,7,10,13,16,19-docosaheptaenoic acid.

an example, the lipoxygenation of the homologue of timnodonic acid, cervonic acid (4,7,10,13,16,19-docosaheptaenoic), is also enhanced by arachidonic acid, but, in contrast with timnodonic acid, it seems able to provide some peroxides by itself, and can indeed partially replace arachidonic acid for potentiating the oxygenation of timnodonic acid (Croset *et al.*, 1988).

Finally, similar potentiations could be observed for the vascular endothelial synthesis of PGI₃ and dihomoprostaglandin (dihomo-PGI₂) from timnodonic and adrenic acids, respectively. Arachidonic acid, as well as its 15-lipoxygenase product, 15-HPETE, were responsible for these stimulations (Bordet *et al.*, 1986, 1988). Fig. 3 summarizes some interactions between fatty acid precursors of oxygenated derivatives.

Conclusion

Metabolic interactions between eicosanoids represent new trends of research in the field of lipid mediators. They are particularly relevant in blood and vascular cells where multiple cell types may interact during their functions. The interactions stated in this review may certainly be extended to various other compounds, but all need to be specified by further studies of their mechanisms, especially concerning the modulation of arachidonic acid metabolism by lipoxygenase products. In addition to those specifications, an overall view of physiological and pathophysiological states should be taken into consideration to ensure the biological relevance of the findings.

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