Mini Review

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Pulmonary intravascular macrophages: prime suspects as cellular mediators of porcine CARPA

Abstract: Pigs provide a highly sensitive and quantitative in vivo model for complement (C) activation-related pseudoallergy (CARPA), a hypersensitivity reaction caused by some state-of-art nanomedicines. In an effort to understand the mechanism of the pigs’ unique sensitivity for CARPA, this review focuses on pulmonary intravascular macrophages (PIMs), which are abundantly present in the lung of pigs. These cells represent a macrophage subpopulation whose unique qualities explain the characteristic symptoms of CARPA in this species, most importantly the rapidly (within minutes) developing pulmonary vasoconstriction, leading to elevation of pulmonary arterial pressure. The unique qualities of PIM cells include the following; 1) they are strongly adhered to the capillary walls via desmosome-like intercellular adhesion plaques, which secure stable and lasting direct exposition of the bulk of these cells to the blood stream; 2) their ruffled surface engaged in intense phagocytic activity ensures efficient binding and phagocytosis of nanoparticles; 3) PIM cells express anaphylatoxin receptors, this way C activation can trigger these cells, 4) they also express pattern recognition molecules on their surface, whose engagement with certain coated nanoparticles may also activate these cells or act in synergy with anaphylatoxins and, finally 5) their high metabolic activity and capability for immediate secretion of vasoactive mediators upon stimulation explain the circulatory blockage and other robust physiological effects that their stimulation may cause. These qualities taken together with reports on liposome uptake by PIM cells during CARPA and the possible presence of these cells in human lung suggests that PIM cells may be a potential therapeutic target against CARPA.

Keywords: adverse immune effects; anaphylatoxins; anaphylaxis; complement; hypersensitivity reactions; nanomedicines; pulmonary intravascular macrophages.

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Introduction: the porcine model of CARPA

Complement activation-related pseudoallergy (CARPA) is a common adverse immune effect of i.v. administered drugs and agents, a subclass of type I hypersensitivity reactions (HSRs) which is not mediated by IgE. CARPA can be caused by a variety of i.v.-administered nanomedicines and antibody-based therapeutic or diagnostic agents, including liposomal drugs, antibodies, polymers, etc. (1, 2). The reaction is usually mild and reversible, but in a small percentage of patients the symptoms are severe or even lethal, which lends substantial clinical and regulatory significance to its study in animal models. A subject of previous reviews, CARPA can be induced in many animal species, among which pigs stand out as being the most appropriate species for mimicking the symptoms and other conditions of the reaction in hypersensitive man (3). Accordingly, the porcine CARPA model has been used in many previous studies on liposome and other nanoparticle-induced CARPA wherein the methods applied, the symptoms and their interrelations and many
other details of the reaction have been amply described (4–8). One of our previous reviews (3) in this volume highlights the variation of cardiovascular symptoms in porcine CARPA, while the present review focuses solely on the likely role of a particular cell in the lung of pigs: pulmonary intravascular macrophages, or PIM cells. The goal is to summarize the information on PIM cells that point to their central role in CARPA. Since PIM cells can also occur in humans, the review highlights the possibility that their selective suppression might be an effective approach to prevent CARPA.

**PIM cells in general**

PIMs are resident cells in the pulmonary capillaries of animals in the Artiodactyla order, such as the pig, sheep, cattle, in the horse of the Perissodactyla order, and also in cats (9). They represent a part of the mononuclear phagocyte system (MPS) in the lung of these animals. Just as Kupffer cells in the liver, they play an important role in the removal of blood-born materials, cellular debris, immune cells, bacteria, viruses, endotoxins, etc. The appearance of these cells varies in different species and their origin and life cycle are debated. One theory holds that they differentiate from circulating peripheral blood mononuclear cells in situ, while others believe that they are immigrants from the neighboring interstitium. In some species PIMs appear as a constitutive member of the lung’s MPS, with colonization starting soon after birth (10, 11).

In species where PIMs are not found at birth, their appearance in the lung can be induced by different effects, for example stimulation with lipopolysaccharides (LPS) or infectious agents, or by changes in the general condition of the organism, such as the presence of hepatic cirrhosis, tumors, hematologic diseases or experimental ligation of the bile duct (12, 13). Pulmonary induction of PIM cells in the lung was described in rats, mice, hamsters, rabbits, chicken, dogs and macaques (14–16).

The species that lack PIMs show no pulmonary hypertension in response to CARPagenic triggers, or need three orders higher doses to indicate the symptoms (17).

The amount and size of PIM cells is in the d=20–80 μm range show wide differences among the species, however, the numbers are difficult to compare directly because of the inconsistent specifications. For example, the amount of PIM cells in the lung of sheep, being the highest, was given as 20% of the endothelial surface, while in pigs it was specified as 14×10^3/mm² of lung parenchyma. Horse PIMs are the largest in size (18–20).

**Morphology**

Figure 1 illustrates the most prominent features of PIM cells: rounded shape, ruffled membrane, presence of pseudopods and adhesion onto the surface.

Other characteristic features include indented nucleus and a unique glycocalyx embedded in the plasma membrane via lipid and lipoprotein foothills of 50–200 nm in size. This surface plays a key role in receptor-mediated endocytosis or phagocytosis of blood-born materials, endotoxins, tracer particles, liposomes (22–25).

**Adherence**

PIMs have a significant ability for adherence, which is one of the most important characteristics of these cells. They firmly attach to the capillary endothelium via junction-like intercellular adhesion plaques (ICAPs), as demonstrated for the case of a sheep PIM cells adhered to the pulmonary capillary endothelium (Figure 2). In addition to pulmonary capillaries, in vitro PIM cells adhere via adhesion plaques to pulmonary artery and corneal and aorta segments (21). The intercellular space between the PIM cell membrane and adherence surface is 15–20 nm and electron dense material is present on both sides of the cell membranes with a width of about 30 nm (26).

As shown in Figure 3, the strong adherence of PIM cells enables their in vitro separation.

![Figure 1: Porcine Pulmonary Intravascular Macrophages (PIM cells).](image-url) 1) PIMs reaching out with pseudopods attached to the surface of plastic coverslip after 1 h incubation (sizebar 2 μm); 2) PIMs showing rounded shape, ruffled membrane. Picture taken after 8 h incubation on the pulmonary artery endothelium ex vivo, sizebar 5 μm. Modified from Ref. (21) with permission.
mentioned, pulmonary PIM cells dominate in pigs, sheep, cattle, horse and cats (9), while hepatic Kupffer cells dominate in rats, rabbit and mice (27, 28). Key difference between PIMs and Kupffer cells is that PIMs response to particle injection with phagocytosis and secretion of vasoconstrictor substances and other mediators (see below), while liver Kupffer cells have huge retention capacity without such secretory capability (27, 28). PIMs have high affinity to endotoxin which can lead to PIM induction, respiratory symptoms, immune reactions, even serious inflammation. Such activation can arise from external and internal LPS, originating in different organs of the body (e.g., intestines).

**Phagocytosis**

PIM cells are capable for highly effective phagocytosis, for example erythrocytes, fibrin and other extracellular matrix components (29). Constitutive PIMs, like those in the pig, sheep, cattle and horse showed similar kinetics of phagocytic activity (30). Post-phagocytic retention of intravenously administered particles (colloid gold, iron oxide, liposomes, etc.) by PIM cells in the lung in pigs, horses and ruminants is substantial (>40%), while rodent PIM cells had <10% of such activity. Liposome retention by pig PIM cells was found to be over 60%. In swine and ruminants the amount of PIMs and the functional activity of phagocytosis show strong correlation (31–33). Several publications show that PIMs are also able to take up viral particles (e.g., hog cholera, African swine fever) during inflammation (34–36).

**Receptors**

Table 1 shows the receptors on the surface of PIM cells along with their molecular type and function. These receptors serve the adhesion and secretory function of PIM cells. From the point of view of CARPA the C5aR is especially important, since it is very likely that it plays a key role in channeling the C activation signal to physiological changes during CARPA. Our literature search has not found direct demonstration of C5aR on PIM cells, but the indirect evidence is overwhelming. It includes the omnipresence of C5aR on monocyte/macrophage line cells and multiple demonstration of C5aR on pulmonary alveolar macrophages (36, 45–49). As mentioned, CARPA represents an anaphylactic reaction, a phenomenon whose name reveals its relation to anaphylatoxins.
Table 1: Receptors on PIM cells.

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Structure</th>
<th>Function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P Integrins</td>
<td>glycosilated-dimeric proteins</td>
<td>– Cell adherence &lt;br&gt;– Intercellular communication &lt;br&gt;– Cell signaling &lt;br&gt;– Regulation of cell shape and motility</td>
<td>(37)</td>
</tr>
<tr>
<td>Toll-like receptors (TLR 1–9)</td>
<td>dimeric protein</td>
<td>Recognition of &lt;br&gt;– Pathogens &lt;br&gt;– LPS &lt;br&gt;– Lipoproteins &lt;br&gt;– Lipopeptides &lt;br&gt;– β-glucan (Zymosan)</td>
<td>(38–40)</td>
</tr>
<tr>
<td>Fc-receptor (FcR)</td>
<td>transmembrane tyrosine kinase</td>
<td>Binding of &lt;br&gt;– IgG, &lt;br&gt;– IgA &lt;br&gt;– IgE &lt;br&gt;– Opsonins</td>
<td>(41, 42)</td>
</tr>
<tr>
<td>Complement-receptors CR1</td>
<td>single-chain membrane glycoproteins</td>
<td>CR1 &lt;br&gt;– binds C3b, C4b, &lt;br&gt;– binds immune complexes &lt;br&gt;– Mediates adherence and phagocytosis, &lt;br&gt;– Inhibits C activation via the classic and alternative pathways &lt;br&gt;CR3 (CD11b/18) &lt;br&gt;– binds iC3b &lt;br&gt;– promotes adhesion to the vascular endothelium &lt;br&gt;– binds β-glucan (Zymosan) &lt;br&gt;– C3dg and C3d bind iC3b with low affinity &lt;br&gt;– CR4 receptor binds iC3b &lt;br&gt;– CR3 (CD11b/18) and CR4 (CD11c/18) are both bind to iC3b. &lt;br&gt;CR3 binds iC3b with high and C3dg and C3d with low affinity. &lt;br&gt;The CR4 receptor binds iC3b but not β-glucan</td>
<td>(43, 44)</td>
</tr>
<tr>
<td>C5aR (C5R1, CD88)*</td>
<td>Membrane spanning</td>
<td>Binding of anaphylatoxin C5a</td>
<td>(36, 45–49)</td>
</tr>
</tbody>
</table>

**Secretory products and mediators**

Following stimulation, PIM cells can secrete a large number of vasoactive and/or inflammatory mediators, listed in Table 2.

Among the secretory products, thromboxane A2 (TXA2) deserves special attention, as it plays a pivotal role in the hemodynamic changes that we see and measure in the porcine CARPA model. The vasoconstrictive and consequent hypertensive effect of TXA2 has been known for long (58, 59), and the causality between these phenomena obtains spectacular demonstration in the porcine CARPA model inasmuch as the rise of PAP closely follows the rise of TXB2 level in blood (TXB2 is the stable metabolite of TXA2) on the second-to minute scale, with only a few second delay (Figure 4). In addition, indomethacin, an inhibitor of cyclooxygenase which produces TXA2, completely inhibits the rise of PAP and other hemodynamic changes (4), which effect offers a possible therapeutic intervention with CARPA. It should also be noted regarding the efficacy of indomethacin that TXA2 secretion and pulmonary vasoconstriction starts in the lung of pigs within 1–3 min after i.v. administration of liposomes or other C-activating nanoparticles (3). Since indomethacin is an effective inhibitor of CARPA even when it is administered only minutes before triggering the reaction (4), TXA2 must be formed by cyclooxygenase in a very fast reaction during CARPA, rather than being stored in preformed intracellular vesicles and released upon PIM cell activation.

In addition to TXB2, PIMs secrete cytokines, oxygen radicals and proteolytic enzymes which contribute to local tissue injury and delayed cardiovascular effects in CARPA and/or inflammation.

**Methodical aspects of experimentation with PIMs**

Table 3 lists the experimental methods applied for addressing various questions relating to PIM cell structure and function.
There are many facts and considerations that suggest that PIM cells play a causal role in porcine CARPA. These include the following:

1. The initial eicosanoid (TXB2) secretion and pulmonary hypertension closely coincide (5);
2. The kinetics of particle uptake by PIM cells is also in the same time course (in minutes) as the development of pulmonary and other hemodynamic changes (29, 66);
3. The species that lack PIMs (or have only induced PIMs under normal conditions, i.e., rats) show systemic hemodynamic changes after i.v. bolus injections of reactogenic drugs (Zymosan, Ambisome) only at 2–3 orders of magnitude higher doses than the reactogenic trigger dose in pigs (17);
4. Depletion of PIM cells eliminates most of the acute abnormal pulmonary hemodynamic changes in endotoxin shock (63) or hyperacute pulmonary xenograft rejection in pigs (49). PIM depletion in sheep led to the loss of pulmonary vaso-responsiveness, whose return coincided with PIM repopulation (67). PIM depletion

### Table 2: PIM cell-derived secretory products and mediators.

<table>
<thead>
<tr>
<th>Mediator type</th>
<th>Structure</th>
<th>Function</th>
<th>References</th>
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<tbody>
<tr>
<td>Thromboxane A2</td>
<td>Eicosanoid</td>
<td>Pulmonary vasoconstriction</td>
<td>(50, 51)</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td></td>
<td></td>
<td>(52)</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>Soluble glycoproteins</td>
<td>proinflammatory, activation of neutrophils</td>
<td>(38, 53–57)</td>
</tr>
<tr>
<td>IL-1beta</td>
<td></td>
<td>proinflammatory, activation of neutrophils</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td>proinflammation, leukocyte activation,</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
<td>promotion of recruitment of Platelets, and heterophils</td>
<td></td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td></td>
<td>induces cell proliferation, migration and angiogenesis</td>
<td></td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td></td>
<td>angiogenesis, vascular permeability increase</td>
<td></td>
</tr>
<tr>
<td>Reactive oxygen species</td>
<td></td>
<td>oxidative tissue injury, vascular tone mediator</td>
<td>(57)</td>
</tr>
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### Figure 4: Time correlation between the rises of blood TXB2 and pulmonary arterial pressure during zymosan-induced CARPA in a pig (reaction following 0.5 mg/kg Zymosan i.v. injection).

Zymosan (0.5 mg/kg) was injected i.v. at time 0. At 30 s after the injection TXB2 level exceeds 9× the preinjection value, and clearly precedes the rise of PAP. Original data reproducing a similar experiment wherein the reaction was triggered by liposomes.
also attenuated capillary leakage, preserved low pulmonary vascular resistance and decreased the production of thromboxane A2 (49);

5. In miniature pig reactogenic liposomes caused CARPA and, at the same time, the authors could detect and visualize the presence of liposomes in PIM cells (66).

### The double hit theory of CARPA

Porcine CARPA has a feature that is difficult to explain: in the case of certain drugs, only the first dose causes HSR; the second, or third similar, or even greater doses remain ineffective. The phenomenon represents self-induced tolerance, or tachyphylaxis. It is observed with PEGylated small unilamellar liposomes, such as Doxil®, certain polymers, but not with highly charged AmBisome, or large multilamellar liposomes. The clinical significance of tachyphylaxis lies in the possibility to tolerize patients against HSR by slow initial administration of the drug in a way the first reaction remains subclinical, and then administering the rest of the dose without adverse event. In fact, the well-known clinical success of low reactogenic administration protocols, applied for antibody-based pharmaceuticals (68–71) and some liposomal drugs, e.g., Doxil® (72) is likely to rests on this principle.

Possible explanations for the phenomenon include the depletion of a reaction mediator (such as natural antibodies), or saturation of a reaction-mediating process (such as C activation or cellular uptake of liposomes) and the “double hit” hypothesis (Figure 5).

According to the “double hit” hypothesis, tachyphylactic CARPA is not only C-activation, and, hence C5aR-dependent, but also depends on cellular uptake of the reactogenic drug by PIM cells, via one or more of their surface receptors (e.g., Fc receptor, Toll-like receptor, or similar pattern recognition receptors). It is only simultaneous occurrence of these processes that can trigger PIM cells for release reaction, and if one activation step is too weak or missing, the reaction will fade and then disappear. It is assumed that in the case of tachyphylactic HSRs one or the other activation channel is irreversible, or get downregulated,

### Table 3: Methods applied in PIM cell research.

<table>
<thead>
<tr>
<th>Research area</th>
<th>Method</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Phagocytic features</td>
<td>tracers used:</td>
<td>(20, 60)</td>
</tr>
<tr>
<td></td>
<td>– monastral blue</td>
<td></td>
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<tr>
<td></td>
<td>– radiolabeled molecules</td>
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<td></td>
<td>– gold colloids</td>
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<td></td>
<td>– magnetic iron oxide</td>
<td></td>
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<tr>
<td></td>
<td>– surfactants</td>
<td></td>
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<tr>
<td></td>
<td>– fluorescent molecules</td>
<td></td>
</tr>
<tr>
<td>Physiologic function</td>
<td>Depletion by</td>
<td>(49, 61–63)</td>
</tr>
<tr>
<td></td>
<td>– gadolinium chloride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– liposomal clodronate</td>
<td></td>
</tr>
<tr>
<td>Isolation/ culturing</td>
<td>Detachment from endothel by</td>
<td>(21, 32, 64, 65)</td>
</tr>
<tr>
<td></td>
<td>– magnetic field treatment after forced phagocytosis of iron oxide</td>
<td></td>
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<tr>
<td></td>
<td>– Enzymatic digestion (collagenase, DNase)</td>
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**Figure 5:** Scheme of the “double hit” hypothesis, explaining tachyphylactic CARPA. PIM cells are activated both via the C3a/C5a receptor (anaphylatoxin receptors, ATr), and via pattern recognizing receptor (PRr)-mediated uptake of Doxil®, illustrating liposomes or other coated nanoparticles that are taken up by these cells. In case of “double hit” simultaneous binding occurs on both receptor types, leading to additive or synergetic stimulation of the cell that entails mediator release and, ultimately, HSR.
explaining the lack of reaction upon the second and later repetitive treatments. In case of non-tachyphylactic reactions full secretory response can be achieved from PIMs either by a strong, supra-threshold stimulus of ATr and/or on PRr receptors, or by simultaneous sub-threshold stimuli on both receptor fields. It leads to tachyphylaxis when the stimulus is way under the effective sub-threshold level. The theory, illustrated in Figure 5, equally applies to mast cells and PIM cells (3). Future studies will hopefully reveal more details about the involvement of PIM cells in CARPA and the mechanism of tachyphylaxis.

Outlook with speculations on the mechanism of human CARPA

Man and nonhuman primates lack constitutive PIMs, although in baboons an increased phagocytic activity is shown in the lung by mononuclear cells (15). Macrophages can, nevertheless, accumulate in the intravascular space in human lungs, for example in the so-called hepatopulmonary syndrome, a common complication of hepatic cirrhosis (25, 56, 73). The mechanism and conditions of de novo PIM cell colonization in human lung is still unknown, and in lack of contrary evidence, it is not excluded that a low percentage of healthy people also host PIM cells in their lung. A further speculation might be that the low percentage of man who develops severe CARPA carry somewhere in their circulation intravascular macrophages (perhaps Kupffer cells) which like PIM cells, immediately respond to exposure to particles and/or anaphylatoxins with intense secretion of allergy mediators into the blood. The bottom line is that the study of the role of PIM cells or other macrophages in CARPA will hopefully shed more light on the pathogenesis of this adverse immune reaction to state-of-art (nano)medicines.

References


**Bionotes**

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Domokos Csukás graduated as a veterinarian in 2005 at the Faculty of Veterinary Science, Szent István University Budapest, Hungary. After 7 years practice in small animal oriented veterinary hospitals he joined the team of the Department of Surgical Research and Techniques in the Faculty of Medicine of Semmelweis University, Budapest. He has special interests in laboratory animal care, animal model development and immune toxicological tests in the field of nanomedicine. He is working on his PhD thesis focusing on the side effects of nanodrugs, and the role of PIM cells in complement activation related pseudoallergy.

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György Wéber received his PhD in medicine in 1992 from University of Pécs, Hungary. He was appointed to professor of surgery in 2003. He is a qualified general and vascular surgeon. In 2010 he founded the Department of Surgical Research and Techniques, Medical Faculty, Semmelweis University, Budapest, Hungary and since then he is the chair of this department. His research is mainly dedicated to nanotechnology and scaffolding in tissue engineering (mesh development for hernia repair etc).

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