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Pharmacologic Factors: Anaesthetic Agents that May Influence Cancer Outcomes: Local Anaesthetics

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Abstract Molecular pathways linking inflammation and cancer have been demonstrated. Local anaesthetics have been shown to possess anti-inflammatory effects. Recent retrospective studies have shown that the application of regional anaesthesia is associated with a reduced risk of metastasis and improved long-term outcomes. The beneficial effect of regional anaesthesia has been attributed to the reduction of the postoperative stress response. Biomolecular actions like reduction of Src activation and ICAM-1 expression can explain some of these benefits observed in cancer surgery with local or regional anaesthesia techniques.

Keywords Local anaesthetics · Cancer · Metastasis · Inflammation · ICAM-1 · Src kinase

Introduction

Recently, there has been a revival in the usage of local anaesthetic agents, which have traditionally been acknowledged for use in pain treatment and cardiac arrhythmias via their property to block the sodium channel. Research has shown that local anaesthetics can interfere with other receptors, leading to new indications, based predominantly on their anti-inflammatory properties. Cancer initiation, development and extension are also most often linked to an inflammatory surrounding. This link between inflammation and cancer has led to the investigation of local anaesthetics for their suitability to improve cancer outcomes. This hypothesis has been supported by some retrospective studies showing prolonged recurrence-free time in patients receiving regional anaesthesia after breast or prostate cancer [1, 2].However, in these studies mechanism either direct or indirect involved in these beneficial effects remained unclear and speculative.

Link Between Inflammation and Cancer

Tumour development, including promotion, malignant conversion, invasion and metastases, is all linked with inflammatory responses at different stages [3]. Inflammation also interferes with the immune system and responses to therapy [4].

Surgery provides a suitable environment to promote the development of cancer, since a strong inflammatory response is present and the immune system is impaired [5]. In fact, it has been shown [6] that an exaggerated perioperative response will exhaust the immune system resulting in multiple organ failure and patient death.

Cancer surgery is associated with inadvertent seeding of tumour cells during the procedure. Reactivation of minimal residual disease and/or pre-existing micro-metastatic disease by perioperative inflammatory responses may lead to cancer recurrence and reduced long-term survival.

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Although there is no clear evidence that circulating tumour cells are associated with distant metastases, experimental studies have shown that such a mechanism can occur [6, 7].

Role of the ICAM-1, Src Protein Tyrosine Kinase and MPC-1 on Inflammation and Cancer Cell Biology

ICAM-1 is a transmembrane glycoprotein containing five Ig-like domains that is a member of the Ig superfamily and is expressed on numerous cell types including leucocytes, endothelial cells, keratinocytes and fibroblasts. This protein serves as a ligand for the membrane-bound integrin receptors LFA-1 or leucocytes and plays an important role in leucocyte–endothelial cell interactions and leucocyte migration [8, 9].

The implication of cell adhesion molecules (CAMs) such as ICAM-1, vascular endothelial CAM-1, E-selectin and P-selectin has been investigated extensively in the inflammation process [10]. CAMs are also involved in tumour progression, [11] and Rosette et al. [12] showed that some circulating tumour cells were able to extravasate to a secondary site using a process similar to inflammatory cells. These similarities may in part explain the link between inflammation and the occurrence of metastasis.

The role of ICAM-1 in tumour invasion in vitro, and in metastases in vivo, has been supported by scientific evidence. It was shown that ICAM-1 expression in primary lesions and increased serum levels in patients with malignant melanoma was linked to a reduction of the disease-free interval and survival rate [13]. Similar results were reported in an investigation that examined the role of ICAM-1 in the invasion of human breast cancer cells [12]. In colorectal cancer, the overexpression of ICAM-1 was an indicator of metastatic potential and poor prognosis [14]. For these reasons, it was suggested that ICAM-1 expression can be used as a biomarker for tumour progression as well as a target for therapeutic interventions [15–17].

The Src family is the largest family of non-receptor protein tyrosine kinase and is responsible for signal transduction during many cellular activities including cytoskeletal alterations, differentiation, cell-type progression, adhesion and migration. Aberrant Src activity has been widely implicated in cancer development [18]. Src protein tyrosine kinase is another potent regulator of endothelial permeability and inflammatory responses in tissue cells [19]. The Src family of non-receptor protein tyrosine kinases plays a critical role in cellular signal transduction pathways, regulating cell division, motility adhesion, angiogenesis and survival. Activation of Src family kinases is common in different human cancers. This system seems to be crucial for the proliferation of tumours, disruption of cell/cell contacts, migration, invasiveness and resistance to apoptosis, and are, therefore, attractive targets for application of anticancer therapeutics [20].

Monocyte chemoattractant protein-1 (MCP-1) plays an important role in inflammation by attracting monocytes and macrophages to the inflammatory site. This protein has strong chemoattractant action on monocytes, T cells and NK cells [21]. Additionally, MCP-1 promotes the transmigration of circulating monocytes into tissues [22]. This protein has been implicated in angiogenesis and tumour proliferation [23]. Cai et al. [24] have demonstrated that MCP-1 levels were elevated in lung cancer patients with bone metastases.

There is increasing evidence that inflammation and cancer pathways are connected [25]. For example, epidemiological studies of patients, and molecular investigations of genetically modified mice, have led to the concept that mechanisms leading to inflammation and cancer may be linked [26–28].

The PI3-K pathway is frequently dysregulated in human cancer and regulates many of the hallmarks of cancer [29•]. There has been a large effort to identify molecules which block this pathway [30, 31]. Src is also considered a potential therapeutic target for the treatment of solid tumours. The role of Src family kinase suppression was investigated in the proliferation, migration and invasion of pancreatic cancer cells [32]. The results showed that Src kinase inhibitors suppressed proliferation and induced cell cycle arrest. Another potent tyrosine kinase inhibitor was shown to provide meaningful clinical benefit to patients with metastatic castration-resistant prostate cancer [33•].

Anti-inflammatory Effects of LA

Currently, it is acknowledged that local anaesthetics are potent anti-inflammatory drugs [34–36]. Their site of action is the G-protein "responsible" for the coupling of membrane receptors to intracellular molecules [37].

It has been shown that local anaesthetics can moderate the regulatory mechanisms of polymorphonuclear leucocytes [38], reduce leucocyte adherence by interfering with integrins [39] and the intercellular adhesion molecule-1 (ICAM-1) [40], influence leucocyte motility by affecting the cytoskeleton [41] or by reducing the release of chemoattracting agents [42]. They have also been shown to inhibit prostaglandin biosynthesis, the release of thromboxane B2 and leukotriene B4 [43], as well as the release of cytokines such as IL-Ia [44], IL-Ib and TNF-α [45] and IL-8 [46].

Blumenthal et al. [47] investigated the effects of ropivacaine in a rat model of LP5-induced acute lung injury, and demonstrated that ropivacaine significantly decreases ICAM-1 expression, reduced leucocyte adhesion and diminished cytotoxicity, suggesting a potential benefit of ropivacaine for the treatment of LPS-induced acute lung injury. Feng et al. [48] investigated the effects of lidocaine in LPS-induced lung injury in rats, and found that lidocaine reduced the lung injury and the subsequent release of TNF-α and IL-6 by inhibiting the NF-κB activation.

A recent investigation examined this mechanism to understand the beneficial effects of ropivacaine in the LPS-induced lung injury model [49••]. Mice were exposed to either nebulized normal saline or lipopolysaccharide in presence or absence of ropivacaine (300 µl of 1 µmol intrathecaly), followed by either normal or high total volume ventilation. The results showed that mice treated with ropivacaine had a significant reduction of excess lung water, extravascular plasma equivalents, permeability index and myeloperoxidase activity. However, the deleterious effects induced by high volume ventilation were not altered by ropivacaine. Western blot analysis of lung homogenates, as well as human lung microvascular endothelial cells treated in culture with lipopolysaccharide alone, showed a significant reduction in Src activation/expression, as well as ICAM-1 expression and caveolin-1 phosphorylation.

It is known that pulmonary endothelial barrier dysfunction mediated in part by Src kinase activation [50, 51] plays a crucial role in acute inflammatory disease. The proinflammatory cytokine tumour necrosis factor-α activates Src protein kinase and consequently increases endothelial permeability [19]. Piegeler et al. [52••] hypothesized that ropivacaine and lidocaine could attenuate inflammatory Src signalling by disrupting the phosphatidylinoside 3-kinase(PI3K)-Akt-nitric oxide pathway, thus blocking Src-dependent neutrophil adhesion and endothelial hyperpermeability in human lung microvascular endothelial cells. The results showed that both ropivacaine and lidocaine were able to attenuate TNF-α-induced neutrophil adhesion and endothelial hyperpermeability via a reduction of Akt, endothelial nitric oxide synthase and Src activation.

In summary, these investigations clearly demonstrate the anti-inflammatory effects of lidocaine and ropivacaine. Moreover, they demonstrate that the beneficial effects of local anaesthetics are even more pronounced when the ICAM-1 and Src are stimulated by lipopolysaccharide or TNF-α, a situation mimicked by the perioperative inflammatory response. It is suggested that inhibition of inflammatory Src signalling by local anaesthetics is accomplished via inhibition of the recruitment of p85 regulatory subunit of PI3K to TNF-α receptor1. This, in turn, prevents P13K activation and subsequent cascade signalling involving phosphorylation/activation of Akt, endothelial nitric oxide synthase, nitric oxide generation and Src activation. Inhibition of Src-dependent intercellular adhesion molecule-1 phosphorylation blocks the increase in neutrophil binding, and the inhibition of direct and indirect (via the phosphorylation of caveolin-1) Src-dependent destabilization of adherence functions attenuates endothelial barrier disruption and hyperpermeability [52].

Effects of LA on Metastasis and Cancer Cell Biology

We recently demonstrated that lidocaine and ropivacaine inhibited inflammatory cytokine-signalling, proliferation and migration of human lung adenocarcinoma cells [53••]. In this in vitro model, NCI-H838 lung cancer cells were incubated with TNF-α or LPS in the absence/presence of ropivacaine or lidocaine at different concentrations. Cell lysates were analysed for Src activation and ICAM-1 phosphorylation. MCP-1 production, cell proliferation and migration were also assessed. The results of this investigation showed that both local anaesthetics inhibited Src activation and ICAM-1 phosphorylation induced by inflammatory mediation TNF-α and LPS in a dose-dependent manner. Additionally, both lidocaine and ropivacaine could be shown to reduce TNF-α-induced MCP-1 production, and inhibit cancer cell proliferation and migration [53]. MMP-9 secretion triggered by TNF-α was also significantly inhibited. Matrix-metalloproteinases are crucial in the pathogenesis of new metastatic sites originating from solid tumours. These enzymes degrade the extracellular matrix and basal lamina, thus allowing malignant cells to extravasate, forming satellite lesions [54, 55]. Other beneficial effects have been demonstrated by Martinsson [56], who found that ropivacaine inhibited the growth of human colon adenocarcinoma cells in a dose-dependent manner, and that this effect was more pronounced with ropivacaine than with lidocaine, although no physiopathological mechanism was suggested. Sakaguchi et al. [57] showed that lidocaine suppressed both serum-induced and epidermal growth factor–induced proliferation at clinical concentrations on human tongue cancer cells. Lucchinetti et al. [58••] investigated the anti-proliferative effects of local anaesthetics on mesenchymal stem cells and the potential implications for tumour spreading and wound healing. They demonstrated that lidocaine, ropivacaine and bupivacaine, at concentrations of 10–100 µM, inhibited the proliferation, colony formation, in vitro wound healing and bone differentiation assays of culture-expanded bone marrow-derived murine mesenchymal stem cells. Their results suggested that

mechanisms involved in this antiproliferative action may involve the inhibition of IκB–NF–κB–ICAM-1 signalling pathway, as well as the inhibition of mitochondrial respiration with adenosine triphosphate depletion. Chang et al. [59] investigated the apoptotic effects of lidocaine and bupivacaine in human breast tumour cells. The treatment showed that both local anaesthetics induced caspase 7,8,9 and poly ADP-ribose polymerase cleavage. The authors concluded that local anaesthetic-induced apoptosis may have beneficial actions in the treatment of breast cancer. Lirk et al. [60] incubated breast cancer cell lines with lidocaine and performed cell counts, determined apoptosis using the TUNEL stain and assessed global methylation status, a process increasingly recognized as a major hallmark of cancer. The authors observed a dose-dependent decrease in DNA methylation in response to lidocaine. Local anaesthetic-induced cytotoxicity was evaluated in vitro in T-lymphoma cells by Werdehausen et al. [61]. A concentration-dependent cytotoxicity was observed for all investigated local anaesthetics. Apoptosis was seen at low concentrations, whereas necrosis was observed at higher concentrations. Tetracaine was shown to have a higher potential for toxicity than lidocaine and mepivacaine. There was no effect of stereoisomerism on apoptosis and necrosis.

In the daily practice, the anti-inflammatory effects of local anaesthetics have already been extensively shown in bowel surgery. Studies (37–40) have demonstrated that infusion of a bolus of lidocaine 1 mg/kg followed by a continuous infusion of 1.5 mg/kg/h resulted in a significant faster recovery of bowel function, shortened hospital stay, reduction of plasma levels of IL-6, IL-8, complement C3a, IL-1 ra and the expression of CD11 B and P-selectin.

Conclusions

Metastatic disease after cancer remains a crucial issue. Traditional systemic therapy is often delayed for weeks after surgery. Recent studies have shown that cellular and molecular mechanisms critical to the metastatic process may be greatly influenced during the perioperative phase [62]. Postoperative inflammatory surroundings have the potential to increase the aggressiveness of circulating tumour cells via mechanisms involving Src activation and ICAM-1 expression. In vitro and in vivo investigations have shown that both lidocaine and ropivacaine have the potential to mitigate this activation. These positive biomolecular effects can interfere with the seeding of postoperatively circulating tumour cells within the soft tissues, thus preventing or reducing the occurrence of distant metastasis. Future prospective, randomized, clinical trials need to be performed to support this hypothesis.

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Compliance with Ethics Guidelines

Conflict of Interest Alain Borgeat, Carl Schick and Gina Votta-Velis declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology. 2006;105:660–4.
2. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology. 2008;109:180–7.
3. Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell. 2005;7:211–7.
4. Lin E, Calvano SE, Lowry SF. Cytokine response in abdominal surgery. In: Schein M, Wise L, editors. Cytokines and the Abdominal Surgeon. Austin: Landes; 1998. p. 17–34.
5. Brochner AC, Toft P. Pathophysiology of the systemic inflammatory response after major accidental trauma. Scand J Trauma Resusc Emerg Med. 2009;17:43.
6. Nishizaki T, Matsumata T, Kanematsu T, Yasunaga C, Sugimachi K. Surgical manipulation of VX2 carcinoma in the rabbit liver evokes enhancement of metastasis. J Surg Res. 1990;49:92–7.
7. Hayashi N, Egami H, Kai M, Kurusu Y, Takano S, Ogawa M. No-touch isolation technique reduces intraoperative shedding of tumor cells into the portal vein during resection of colorectal cancer. Surgery. 1999;125:369–74.
8. Scauton DE, Marlin SD, Stratowa C, Dustin ML, Springer TA. Primary structure of ICAM-I demonstrates interaction between members of the immunoglobulin and integrin supergene families. Cell. 1998;52(6):925–33.
9. Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell. 1994;76:301.
10. Kim I, Moon SO, Kim SH, Kim HJ, Koh YS, Koh GY. Vascular endothelial growth factor expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin through nuclear factor-kappa B activation in endothelial cells. J Biol Chem. 2001;276:7614–20.
11. Johnson JP. Cell adhesion molecules in the development and progression of malignant melanoma. Cancer Metastasis Rev. 1999;18:345–57.
12. Rosette C, Roth RB, Oeth P, et al. Role of ICAM1 in invasion of human breast cancer cells. Carcinogenesis. 2005;26:943–50.
13. Kageshita T, Yoshii A, Kimura T, et al. Clinical relevance of ICAM-1 expression in primary lesions and serum of patients with malignant melanoma. Cancer Res. 1993;53:4927–32.

14. Natali PG, Hamby CV, Felding-Habermann B, et al. Clinical significance of alpha(v)beta3 integrin and intercellular adhesion molecule-1 expression in cutaneous malignant melanoma lesions. Cancer Res. 1997;57:1554–60.
15. Hayes SH, Seigel GM. Immunoreactivity of ICAM-1 in human tumors, metastases and normal tissues. Int J Clin Exp Pathol. 2009;2:553–60.
16. Maruo Y, Gochi A, Kaihara A, et al. ICAM-1 expression and the soluble ICAM-1 level for evaluating the metastatic potential of gastric cancer. Int J Cancer. 2002;100:486–90.
17. Huang WC, Chan ST, Yang TL, Tzeng CC, Chen CC. Inhibition of ICAM-1 gene expression, monocyte adhesion and cancer cell invasion by targeting IKK complex: molecular and functional study of novel alpha-methylene-gamma-butyrolactone derivatives. Carcinogenesis. 2004;25:1925–34.
18. Fizazi K. The role of Src in prostate cancer. Ann Oncol. 2007;18:1765–73.
19. Hu G, Minshall RD. Regulation of transendothelial permeability by Src kinase. Microvasc Res. 2009;77:21–5.
20. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. Cancer Metastasis Rev. 2003;22:337–58.
21. Rollins BJ. Monocyte chemoattractant protein 1: a potential regulator of monocyte recruitment in inflammatory disease. Mol Med Today. 1996;2:198–200.
22. Rollins BJ, Walz A, Baggiolini M. Recombinant human MCP-1/JE induces chemotaxis, calcium flux, and the respiratory burst in human monocytes. Blood. 1991;78:1112–6.
23. Goede V, Brogelli L, Ziche M, Augustin HG. Induction of inflammatory angiogenesis by monocyte chemoattractant protein-1. Int J Cancer. 1999;82:765–70.
24. Cai Z, Chen Q, Chen J, et al. Monocyte chemotactic protein 1 promotes lung cancer-induced bone resorptive lesions in vivo. Neoplasia. 2009;11:228–36.
25. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436–44.
26. Gottschalk A, Brodner G, Van Aken HK, Ellger B, Althaus S, Schulze HJ. Can regional anaesthesia for lymph-node dissection improve the prognosis in malignant melanoma? Br J Anaesth. 2012;109:253–9.
27. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357:539–45.
28. Karin M. Nuclear factor-kappaB in cancer development and progression. Nature. 2006;441:431–6.
29. • Sheppard K, Kinross KM, Solomon B, Pearson RB, Phillips WA. Targeting PI3 kinase/AKT/mTor signaling in Cancer. Crit Rev Oncog. 2012;17:69–95. *PI3-κ pathway is frequently dysregulated in human cancer.*
30. Bruhn MA, Pearson RB, Hannan RD, Sheppard KE. AKT-independent PI3-K signaling in cancer-emerging role for SGK3. Cancer Manag Res. 2013;5:281–92.
31. Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K inhibitors: lessons learned from early clinical trials. Rev Clin Oncol. 2013;10:143–53.
32. Je DW, Ji YG, Cho Y, Lee DH. The inhibition of Src family kinase suppresses pancreatic cancer cell proliferation, migration, and invasion. Pancreas. 2014;43:768–76.
33. • Araujo JC, Trudel GC, Paliwal P. Long-term use of dasatinib in patients with metastatic castration-resistant prostate cancer after receiving the combination of dasatinib and docetaxel. Cancer Manag Res. 2013;6:25–30. *Src kinase inhibitors suppressed proliferation and induced cell cycle arrest in prostate cancer.*
34. Hollmann MW, Durieux ME. Local anesthetics: effects on inflammation, wound healing and coagulation. Prog Anesthesiol. 2000;14:291–304.
35. Hollmann MW, Durieux ME. Local anesthetics: effects on the central nervous system and bronchial reactivity. Prog Anesthesiol. 2000;14:323–36.
36. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology. 2000;93:858–75.
37. Hollmann MW, Difazio CA, Durieux ME. Ca-signaling G--protein-coupled receptors: a new site of local anesthetic action? Reg Anesth Pain Med. 2001;26:565–71.
38. Krause KH, Demaurex N, Jaconi M, Lew DP. Ion channels and receptor-mediated Ca2+ influx in neutrophil granulocytes. Blood Cells. 1993;19:165–73.
39. Martinsson T, Oda T, Fernvik E, Roempke K, Dalsgaard CJ, Svensjo E. Ropivacaine inhibits leukocyte rolling, adhesion and CD11b/CD18 expression. J Pharmacol Exp Ther. 1997;283:59–65.
40. Lan W, Harmon DC, Wang JH, Shorten GD, Redmond PH. Activated endothelial interleukin-1beta, -6, and -8 concentrations and intercellular adhesion molecule-1 expression are attenuated by lidocaine. Anesth Analg. 2005;100:409–12.
41. Raucher D, Sheetz MP. Phospholipase C activation by anesthetics decreases membrane-cytoskeleton adhesion. J Cell Sci. 2001;114:3759–66.
42. Li CY, Tsai CS, Hsu PC, Chueh SH, Wong CS, Ho ST. Lidocaine attenuates monocyte chemoattractant protein-1 production and chemotaxis in human monocytes: possible mechanisms for its effect on inflammation. Anesth Analg. 2003;97:1312–6.
43. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. Acta Anaesthesiol Scand. 2006;50:265–82.
44. Sinclair R, Eriksson AS, Gretzer C, Cassuto J, Thomsen P. Inhibitory effects of amide local anaesthetics on stimulus-induced human leukocyte metabolic activation, LTB4 release and IL-1 secretion in vitro. Acta Anaesthesiol Scand. 1993;37:159–65.
45. Gallos G, Jones DR, Nasr SH, Emala CW, Lee HT. Local anesthetics reduce mortality and protect against renal and hepatic dysfunction in murine septic peritonitis. Anesthesiology. 2004;101:902–11.
46. Lahav M, Levite M, Bassani L, et al. Lidocaine inhibits secretion of IL-8 and IL-1beta and stimulates secretion of IL-1 receptor antagonist by epithelial cells. Clin Exp Immunol. 2002;127:226–33.
47. Blumenthal S, Borgeat A, Pasch T, et al. Ropivacaine decreases inflammation in experimental endotoxin-induced lung injury. Anesthesiology. 2006;104:961–9.
48. Feng G, Liu S, Wang GL, Liu GJ. Lidocaine attenuates lipopolysaccharide-induced acute lung injury through inhibiting NF-kappaB activation. Pharmacology. 2008;81:32–40.
49. •• Piegeler T, Dull RO, Hu G, et al. Ropivacaine attenuates endotoxin plus hyperinflation-mediated acute lung injury via inhibition of early-onset Src-dependent signaling. BMC Anesthesiol. 2014;14:57. *Ropivacaine reduces excess lung water, extravascular plasma equivalents, permeability index and myeloperoxidase activity.*
50. Johnson ER, Matthay MA. Acute lung injury: epidemiology, pathogenesis, and treatment. J Aerosol Med Pulm Drug Deliv. 2010;23:243–52.
51. Bhattacharya J, Matthay MA. Regulation and repair of the alveolar-capillary barrier in acute lung injury. Annu Rev Physiol. 2013;75:593–615.
52. •• Piegeler T, Votta-Velis EG, Bakhshi FR, et al. Endothelial barrier protection by local anesthetics. Anesthesiology. 2014;120:1414–28. *Ropivacaine and lidocaine attenuate tumour necrosis factor-α-induced neutrophil adhesion and endothelial hyperpermeability* via *a reduction of Akt, endothelial nitric oxide synthase and Src activation.*
53. •• Piegeler T, Votta-Velis EG, Liu G, et al. Antimetastatic potential of amide-linked local anesthetics: inhibition of lung adenocarcinoma cell migration and inflammatory Src signaling

independent of sodium channel blockade. Anesthesiology. 2012;117:548–59. *Lidocaine and ropivacaine inhibit inflammatory cytokine-signalling, proliferation and migration of human lung adenocarcinoma cells.*

54. Nicoud IB, Jones CM, Pierce JM, et al. Warm hepatic ischemia-reperfusion promotes growth of colorectal carcinoma micrometastases in mouse liver via matrix metalloproteinase-9 induction. Cancer Res. 2007;67:2720–8.
55. Muller-Edenborn B, Roth-Z'graggen B, Bartnicka K, et al. Volatile anesthetics reduce invasion of colorectal cancer cells through down-regulation of matrix metalloproteinase-9. Anesthesiology. 2012;117:293–301.
56. Martinsson T. Ropivacaine inhibits serum-induced proliferation of colon adenocarcinoma cells in vitro. J Pharmacol Exp Ther. 1999;288:660–4.
57. Sakaguchi M, Kuroda Y, Hirose M. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. Anesth Analg. 2006;102:1103–7.
58. •• Lucchinetti E, Awad AE, Rahman M, et al. Antiproliferative effects of local anesthetics on mesenchymal stem cells: potential implications for tumor spreading and wound healing. Anesthesiology. 2012;116:841–56. *Local anaesthetics impaired proliferation, differentiation and respiration and were cytotoxic to murine mesenchymal stem cells* in vitro.
59. Chang YC, Liu CL, Chen MJ, et al. Local anesthetics induce apoptosis in human breast tumor cells. Anesth Analg. 2014;118:116–24.
60. Lirk P, Berger R, Hollmann MW, Fiegl H. Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines in vitro. Br J Anaesth. 2012;109:200–7.
61. Werdehausen R, Braun S, Fazeli S, et al. Lipophilicity but not stereospecificity is a major determinant of local anaesthetic-induced cytotoxicity in human T-lymphoma cells. Eur J Anaesthesiol. 2012;29:35–41.
62. Peach G, Kim C, Zacharakis E, Purkayastha S, Ziprin P. Prognostic significance of circulating tumour cells following surgical resection of colorectal cancers: a systematic review. Br J Cancer. 2010;102:1327–34.