Gout and Hyperuricemia

Review

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The relationships between components of gouty inflammation and cancers

Shun-Jen Chang[1,*]

Purpose: Gout is a chronic inflammatory disease, and gout patients are more likely to develop cancer; here, we review the relationship between the components of gouty inflammation and cancer.

Findings: Multiple steps are required to evoke gouty inflammation, including recognition and uptake of monosodium urate (MSU), ion exchange, inflammasome activation and release of interleukin (IL)-1β and IL-8. Most of the components related to gouty inflammation are associated with carcinogenesis, such as Toll-like receptor (TLR) 2, TLR4, ATP, connexins, pannexins, NLR family pyrin domain containing 3 (NLRP3) inflammasome, IL-1β and IL-8. Controversially, evidence also suggests that TLRs, connexins, NLRP3 inflammasome and IL-1β may be double-edged-swords in the influence of tumor progression.

Conclusion: Most of the components of gouty inflammation are related to carcinogenic, but some of the components exert promoting or inhibiting effects depending different tissues, stages and specific types of cancers.

Key words: Gout; Cancer; Inflammation; Carcinogenesis

[1]National University of Kaohsiung, Department of Kinesiology, Health and Leisure Studies, Kaohsiung, Taiwan.

*Corresponding author:
Prof. Shun Jen Chang
National University of Kaohsiung, Department of Kinesiology, Health and Leisure Studies, Kaohsiung, Taiwan.
E-mail: changsj1104@gmail.com
Tel: +886-7-5916679

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Introduction

Gout is initially caused by deposit of monosodium urate (MSU) in joint spaces followed by induction of inflammatory reaction. Besides hyperuricemia, multiple steps are needed to evoke inflammatory reaction in gout: (1) Recognition of MSU crystals by Toll-like receptor (TLR) 2 or TLR4. (2) Uptake of MSU by macrophages via TLR2/TLR4 recognition or lipid sorting. (3) Activation of the NRLP3 inflammasome. (4) Release of interleukin (IL)-1β. (5) Activation of endothelial IL-1β receptor (IL-1R). (6) Release IL-8 for neutrophil recruitment. Each step is required to trigger gouty attack. Gout patients are more likely to have cancer. Studies show male gout patients tend to have urinary track cancer such as renal, bladder, and prostate cancers [1,2]. Moreover, some studies also found female gout patients with disease onset at less than 50 years old were more likely to have renal [1], liver and colorectal cancer [3]. There was no significant association for those with gout onset over 50 years old.

Since gout disease is a chronic inflammatory disease, it is more like to be associated with higher cancer incidence. Moreover, the heritability of gouty inflammation is higher than hyperuricemia. Therefore, the purpose is to review the relationship between genetic components of gouty inflammation and cancer.

The relationship between phagocytosis of urate and cancer

Phagocytosis of urate is the key step to initial inflammatory reaction. There are many pathways for MSU crystals to enter cells. The first pathway is lipid sorting, where uric acid crystals could directly engage cellular membranes, particularly with the cholesterol components [4]. The second is through Toll-like receptors (TLRs) pathway. MSU crystals were recognized by TLR4 [5]. Zhao et al. revealed ten TLRs exist in humans: TLR1, TLR2, TLR4, TLR5 and TLR6 are expressed on cell surface, and TLR3, TLR7, TLR8 and TLR9 are found exclusively within endosomes [6]. TLR2 and TLR4 recognize MSU and lipopolysaccharides (LPS) which are involved

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in gout inflammation. Increased expressions of TLRs 4 and 9 have been correlated with cancer malignancy [7,8]. Moreover, recent studies have shown the involvement of TLR in the pathogenesis of hepatocellular carcinoma [9], colorectal cancer [10], and pancreatic cancer [11,12] (Table 1). Furthermore, Chang et al. identified Helicobacter pylori can signal through several TLRs, especially TLR2 and TLR4, which is associated with gastric cancer and is considered an important gastric cancer cofactor [13]. Their study further revealed that H pylori induces invasion and angiogenesis through TLRs 2 and 9. TLRs are also associated with several tumor types, especially TLR2, which plays a role in the development of laryngeal carcinoma [14] and epidermal tumors [15]. TLR4 has been found to be associated with tumor pathogenesis [16]. Evidence also show TLR4 enhances metastatic potential through transforming growth factor β [17], and involved in bladder cancer [18] and gastric cancer [19].

Controversially, many TLRs also contribute to tumor suppression, including TLRs 3, 4, 5 and 7 [6], which might prevent the growth of prostate cancer [6]. TLR3 mRNA level was clearly enhanced in prostate cancer cells by stimulating with poly (I:C), which suggests a functional role of TLR3 in prostate cancer [20]. Paone et al. found TLR3 activation directly triggers apoptosis of human prostate cancer cells [21].

On considering another component for MSU phagocytosis, we previously found the cyclic GMP-dependent protein kinase gene (cGKII; PRKG2) is associated with gout [22], and regulates THP-1 (M1) phagocytosis function via TLR2, but not TLR4, to enhance phagocytosis of MSU [23]. Regarding oncogenesis, Wang et al. demonstrated cGKII has an anti-proliferative and pro-differentiation role in mouse colon [24]. The homeostatic functions of cGKII were reproducible in colon cancer cell lines, and downregulation of Sox9 is a possible mechanism [24]. Another carcinogenic effect is related to gastric cancer through inhibiting Rho A activation [25]. Wu et al. suggested that cGKII inhibits epidermal growth factor (EGF) induced signal transduction of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) mediated pathway and further confirms that cGKII may be a cancer inhibitor [26].

The relationship between ATP, connexin/pannexin hemi-channels and cancer

Phagocytosis of MSU crystals leads to the generation of reactive oxygen species (ROS) through activation of NADPH oxidases and may also induce the secretion of ATP, which in turn activates P2X purinoceptor 7 (P2X7R) to cause rapid exit of intracellular potassium that triggers the NLR family pyrin domain containing 3 (NLRP3) inflammasome activation. ATP plays a fundamental role in cellular communication, with its extracellular accumulation triggering purinergic signaling cascades in a diversity of cell types. In the extracellular environment, ATP has a short life due to its enzymatic conversion [27], and ATP activity is mediated by the activation of purinergic P2 receptors, which are associated with chronic inflammation [28]. Moreover, ATP is linked to innate and adaptive immune responses [27,29], and evidence also showed

Table 1. The summary of relationships between components of gouty inflammation and cancer.

Components	Cancer type	Description	References
TLRs	Hepatocellular carcinoma	Pathogenesis	[9]
	Colorectal cancer	Pathogenesis	[10]
	Pancreatic cancer	Pathogenesis	[11,12]
TLR2	Gastric cancer	Association	[13]
TLR3	Prostate cancer cells	Triggers apoptosis	[21]
	Gastric cancer	Association	[13,19]
TLR4	Bladder cancer	Association	[18]
cGKII	Gastric cancer cells	Cancer inhibitor	[26]
Connexins	Tumor cells	Potential factors determining the invasive and metastatic progression.	[40]
	Breast cancer	Context-dependent suppressors and facilitators of progression	[41]
Cx43	Lung tumor	Tumor suppressive roles	[48,49]
Pannexins (Panx1)	Gallbladder carcinomas	Negatively correlated with proliferation	[61]
NLRP3 inflammasome	Colorectal cancer	Deletion of the inflammasome exacerbate metastatic growth.	[71]
IL-1β	Breast, lung, prostate, bladder and colon cancers	Through regulating nitric oxide synthase expression	[81-85]
IL-8	Non-small cell lung cancer	Association	[89]
	Colorectal cancers	Potential diagnosis marker	[94-97]
	Pancreatic cancer	Overexpressed in tumor tissue	[98]

exogenous ATP can control cellular and tissue defense or repair processes via signaling through P1, P2X, and P2Y purinergic receptors. P2X7 signaling has been found to be associated with tumor growth and metastasis [30-34].

Multiple mechanisms have been proposed to regulate ATP release through connexin (Cx) hemichannels and pannexin (Panx) channels [35]. There are 21 connexins and 3 pannexins in the human genome, making it challenging to generalize their function in gout disease and cancer. Cancer is one of the first pathologies found to be associated with gap junction channel impairment, and connexins have long been shown to possess tumor suppressive function, [36] as well as other members of the connexin family such as Cx26 and Cx32 [37-39]. However, connexin expression has been positively correlated with more invasive cancers and metastases [40,41] (Table 1). Mutations of connexins or loss of functional channels are implicated in many diseases and disorders, including congenital deafness, skin disorders, cataracts and cancers [42,43]. Jean et al. suggested a double-edged sword theory for connexins where they would support a tumor suppressor role in early stages of cancer progression, but have an opposing role in late-stage or advanced cancer and metastasis [44].

Loewenstein and Kanno postulated that liver cancer cells were different from normal liver cells in that they lacked intercellular communication [45]. Since then, there have been numerous studies dedicated to uncovering the role of gap junctions and connexins in tumor progression [42,46,47]. Clinical studies have also reported that deficient or abnormal connexins are frequently found in tumor tissues and cell lines, such as breast cancer, prostate cancer, lung cancer, and many other cancer types [43]. In vivo studies demonstrate the tumor suppressive roles of Cx43 and Cx32. Mice with decreased expression of Cx43 or Cx32 exhibit increased carcinogen induced tumor growth in comparison to control wild-type mice, represented by an increase in number and size of tumor nodules in the lung [48,49]. Moreover, Cx43 also showed marked elevation at both RNA and protein levels in cells with increased metastatic potential [50].

The main function of pannexins is to form large-pore single membrane channels for the release of ATP and other metabolites important for cellular communication and autocrine/paracrine signaling [51-56]. Panx1 has been reported to be ubiquitously expressed in most mammalian cells and tissues [51,57]. At the protein level, Panx1 expression is listed in 17 out of 20 tumor types, especially in colorectal, lung, urothelial and stomach cancers [58]. Furlow et al. showed that breast cancer cells expressing the mutant Panx1, increase ATP release in vitro and in vivo under conditions of membrane stretch where the mechano-sensitive Panx1 channel is activated [59]. Furthermore, they proposed that cells expressing mutant Panx1 have a survival advantage in metastatic progression since the ATP released acts on purinergic receptors (P2Y) to suppress apoptosis and reduce cell death in those tight spots of the microvasculature. It also act as a tumor promoting factor implicated in cancer progression, angiogenesis, invasion and metastasis [60].

Regarding Panx1 immunostaining, Schalper et al. concluded that Panx1 expression was negatively correlated with proliferation in gallbladder carcinomas [61]. While Panx1 and Panx3 are expressed in normal adult human facial skin, their expression is not detectable in either basal or squamous cell carcinomas immunestained with anti-pannexin antibodies. Jean et al. concluded that majority of studies point towards a tumor promoting effect of Panx1 expression, and this effect may be different for the other pannexin members on condition of different tissues and cancers [44].

The relationship between NLRP3 inflammasome and cancer

NLRP3 has been shown to act in a multiprotein complex termed the NLRP3 inflammasome, which is composed of NLRP3, the adaptor molecule apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) as well as the cysteine protease caspase-1 [62]. Two signal models have been proposed to activate NLRP3 inflammasome and explain the regulation of IL-1β production [63]. The first model involves the synthesis of pro-IL-1β and NLRP3 which is triggered by transcriptional induction via ligands for TLRs. The stimulus leads to inflammasome oligomerization, resulting in the cleavage of pro-caspase-1, and then release of the mature IL-1β. The second signal is induced by a broad variety of either pathogen-associated molecular patterns (PAMPs) or danger associated molecular patterns (DAMPs). Activation of the NLRP3 inflammasome results in the assembly of scaffold components such as the cytoplasmic receptor NLRP3, the adaptor protein ASC and the effector protein caspase-1 [62,64-68], which in turn cleaves pro-IL-1β to produce biologically active IL-1β.

NLRP3 inflammasomes have been linked to many human diseases, including inflammatory bowel disease and colitis-associated cancer [69,70]. Deletion of the inflammasome component of NLRP3 has shown to exacerbate colorectal cancer metastatic growth [71]. Other molecular

networks take part in nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)-driven inflammation, such as the described NLRP3 inflammasome, even a number of inflammasomes have been identified related to inflammation, the NLRP3 inflammasome has been found associated with tumor development [72,73], but controversy exists from different models [74,75].

The relationships between IL-1β and IL-8 release and cancer

Three gene products of IL-1 family have been thoroughly studied, including two agonistic proteins, IL-1α and IL-1β, and one antagonistic protein, the IL-1Ra. It is well known that the addition of MSU crystals to mononuclear phagocytes induces IL-1β secretion [76,77], and Joosten's study further builds on the concept that MSU crystals need a second signal to induce active IL-1β, which explains why constitutionally-derived metabolic events initiate attacks of gout via the induction of IL-1β mediated joint inflammation [78]. Terkeltaub et al. then demonstrated treatment with IL-1β blockade in gout patients have an impressive and sustained reduction in recurrent attacks of gouty arthritis [79].

Regarding IL-1β in relation to carcinogenesis, Hellwig-Burgel et al. described IL-1β and tumor necrosis factor (TNF) as the cytokines that increase hypoxia-inducible factor-1 (HIF-1) activity in the human hepatoma cell line [80]. IL-1β and TNF are important regulators of inducible nitric oxide synthase (iNOS) which show increased expression in a variety of human malignant tumors, including breast [81], lung [82], prostate [83], bladder [84] and colon [85] cancers (Table 1), and malignant melanoma. However, numerous reports suggest that iNOS expression also has anti-tumor effects. It may be postulated that the final effect of NO on cancer cells depends on its local concentration, the NO source, and the tumor microenvironment [86].

Nonetheless, IL-1β was reported to promote tumor cell growth and metastasis by inducing several pro-metastatic genes such as matrix metalloproteinases and endothelial adhesion molecules, as well as transforming growth factor (TGF)-β, chemokines and growth factors [87]. Moreover, evidence showed sustained induction of IL-1β enhances the intensity of the inflammatory response which can create an inflammatory micro-environment for tumor initiation or promotion [88]. Bhat et al. showed the genotype of IL-1β C31T was significantly associated with increased risk of non-small cell lung cancer [89], whereas Azad et al. found that IL-1β plays an important role in various inflammatory diseases including lung cancer [90].

Furthermore, neutrophil activation and recruitment play a key role in the acute inflammatory response to MSU crystals. Evidence show that MSU have dual effects on neutrophils – activation of IL-8 production and downregulation of myeloid inhibitory C-type lectin expression (MICL) [91]; both IL-8 and MICL may play a pathogenic role in gout by enhancing neutrophil effector functions [92,93].

Concerning the carcinogenic effects of IL-8, several studies have evaluated the application of IL-8 in the diagnosis of colorectal cancers; however, the results are contradictory [94-97] (Table 1). A meta-analysis study performed by Jin et al. concluded that serum IL-8 is a promising biomarker for colorectal cancer detection. Moreover, Xie suggested the mechanisms for IL-8 involvement in carcinogenesis were through its potential functions as a mitogenic, angiogenic, and motogenic factor, which may contribute to tumor cell proliferation, angiogenesis, and migration directly or indirectly [98].

Conclusion

To our knowledge, most of the components related to gouty inflammation can create risk associations with carcinogenesis, such as TLR2, TLR4, ATP, connexins, pannexins, NLRP3 inflammasome, IL-1β and IL-8. Controversially, evidence suggests that TLRs, connexins, NLRP3 inflammasome and IL-1β play a double-edged-sword role in its influence on tumor progression. However, cancer is a complex disease; I propose that the components of gouty inflammation exert promoting or inhibiting effects on carcinogenesis depending on different tissues, stages and specific types of cancer.

References

1.Boffetta P, Nordenvall C, Nyren O, Ye W. A prospective study of gout and cancer. Eur J Cancer Prev. 2009; 18: 127-32.
2.Chen CJ, Yen JH, Chang SJ. Gout patients have an increased risk of developing most cancers, especially urological cancers. Scand J Rheumatol. 2014; 43: 385-90.
3.Chan Y, Hsieh M, Chen C, Chang S. Female gout patients have higher risk of suffering from all cause cancer. Gout and Hyperuricemia. 2016; 3: 93-9.
4.Ng G, Sharma K, Ward SM, et al. Receptor-independent, direct membrane binding leads to cell-surface lipid sorting and Syk kinase activation in dendritic cells. Immunity. 2008; 29: 807-18.
5.Chen L, Wang T, Zhou P, et al. TLR engagement prevents transplantation tolerance. Am J Transplant. 2006; 6: 2282-91.
6.Zhao S, Zhang Y, Zhang Q, Wang F, Zhang D. Toll-like receptors and prostate cancer. Front Immunol. 2014; 5: 352.

7.Fukata M, Chen A, Vamadevan AS, et al. Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. Gastroenterology. 2007; 133: 1869-81.
8.Goto Y, Arigami T, Kitago M, et al. Activation of Toll-like receptors 2, 3, and 4 on human melanoma cells induces inflammatory factors. Mol Cancer Ther. 2008; 7: 3642-53.
9.Dapito DH, Mencin A, Gwak GY, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell. 2012; 21: 504-16.
10.Fukata M, Abreu MT. Role of Toll-like receptors in gastrointestinal malignancies. Oncogene. 2008; 27: 234-43.
11.Ochi A, Graffeo CS, Zambirinis CP, et al. Toll-like receptor 7 regulates pancreatic carcinogenesis in mice and humans. J Clin Invest. 2012; 122: 4118-29.
12.Ochi A, Nguyen AH, Bedrosian AS, et al. MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. J Exp Med. 2012; 209: 1671-87.
13.Chang YJ, Wu MS, Lin JT, Chen CC. Helicobacter pylori-Induced invasion and angiogenesis of gastric cells is mediated by cyclooxygenase-2 induction through TLR2/TLR9 and promoter regulation. J Immunol. 2005; 175: 8242-52.
14.Wang X, Wang J, Liu L, Liang G, Chen X, Xu X. [Expression and clinical significance of TLR2 in laryngeal carcinoma tissue]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2013; 27: 629-32.
15.Weng H, Deng Y, Xie Y, Liu H, Gong F. Expression and significance of HMGB1, TLR4 and NF-kappaB p65 in human epidermal tumors. BMC Cancer. 2013; 13: 311.
16.Oblak A, Jerala R. Toll-like receptor 4 activation in cancer progression and therapy. Clin Dev Immunol. 2011; 2011: 609579.
17.Zhou YH, Liao SJ, Li D, et al. TLR4 ligand/H(2)O(2) enhances TGF-beta1 signaling to induce metastatic potential of non-invasive breast cancer cells by activating non-Smad pathways. PLoS One. 2013; 8: e65906.
18.Wang YH, Cao YW, Yang XC, et al. Effect of TLR4 and B7-H1 on immune escape of urothelial bladder cancer and its clinical significance. Asian Pac J Cancer Prev. 2014; 15: 1321-6.
19.Wang TR, Peng JC, Qiao YQ, et al. Helicobacter pylori regulates TLR4 and TLR9 during gastric carcinogenesis. Int J Clin Exp Pathol. 2014; 7: 6950-5.
20.Harashima N, Inao T, Imamura R, Okano S, Suda T, Harada M. Roles of the PI3K/Akt pathway and autophagy in TLR3 signaling-induced apoptosis and growth arrest of human prostate cancer cells. Cancer Immunol Immunother. 2012; 61: 667-76.
21.Paone A, Starace D, Galli R, et al. Toll-like receptor 3 triggers apoptosis of human prostate cancer cells through a PKC-alpha-dependent mechanism. Carcinogenesis. 2008; 29: 1334-42.
22.Chang SJ, Tsai MH, Ko YC, Tsai PC, Chen CJ, Lai HM. The cyclic GMP-dependent protein kinase II gene associates with gout disease: identified by genome-wide analysis and case-control study. Ann Rheum Dis. 2009; 68: 1213-9.
23.Liao WT, You HL, Li C, Chang JG, Chang SJ, Chen CJ. Cyclic GMP-dependent protein kinase II is necessary for macrophage M1 polarization and phagocytosis via toll-like receptor 2. J Mol Med (Berl). 2015; 93: 523-33.
24.Wang R, Kwon IK, Thangaraju M, et al. Type 2 cGMP-dependent protein kinase regulates proliferation and differentiation in the colonic mucosa. Am J Physiol Gastrointest Liver Physiol. 2012; 303: G209-19.
25.Wang Y, Chen Y, Li Y, Lan T, Qian H. Type II cGMPdependent protein kinase inhibits RhoA activation in gastric cancer cells. Mol Med Rep. 2014; 9: 1444-52.
26.Wu M, Wu Y, Lan T, Jiang L, Qian H, Chen Y. Type II cGMPdependent protein kinase inhibits EGFinduced JAK/STAT signaling in gastric cancer cells. Mol Med Rep. 2016; 14: 1849-56.
27.Eltzschig HK, Sitkovsky MV, Robson SC. Purinergic signaling during inflammation. N Engl J Med. 2012; 367: 2322-33.
28.Idzko M, Ferrari D, Eltzschig HK. Nucleotide signalling during inflammation. Nature. 2014; 509: 310-7.
29.Junger WG. Immune cell regulation by autocrine purinergic signalling. Nat Rev Immunol. 2011; 11: 201-12.
30.Burnstock G, Verkhratsky A. Long-term (trophic) purinergic signalling: purinoceptors control cell proliferation, differentiation and death. Cell Death Dis. 2010; 1: e9.
31.White N, Burnstock G. P2 receptors and cancer. Trends Pharmacol Sci. 2006; 27: 211-7.
32.Dixon CJ, Bowler WB, Fleetwood P, Ginty AF, Gallagher JA, Carron JA. Extracellular nucleotides stimulate proliferation in MCF-7 breast cancer cells via P2-purinoceptors. Br J Cancer. 1997; 75: 34-9.
33.Adinolfi E, Pizzirani C, Idzko M, et al. P2X(7) receptor: Death or life? Purinergic Signal. 2005; 1: 219-27.
34.Adinolfi E, Raffaghello L, Giuliani AL, et al. Expression of P2X7 receptor increases in vivo tumor growth. Cancer Res. 2012; 72: 2957-69.
35.Lohman AW, Isakson BE. Differentiating connexin hemichannels and pannexin channels in cellular ATP release. FEBS Lett. 2014; 588: 1379-88.
36.Mesnil M. Connexins and cancer. Biol Cell. 2002; 94: 493-500.
37.Cronier L, Crespin S, Strale PO, Defamie N, Mesnil M. Gap junctions and cancer: new functions for an old story. Antioxid Redox Signal. 2009; 11: 323-38.
38.Sato H, Hagiwara H, Ohde Y, Senba H, Virgona N, Yano T. Regulation of renal cell carcinoma cell proliferation, invasion and metastasis by connexin 32 gene. J Membr Biol. 2007; 216: 17-21.
39.Nojima H, Ohba Y, Kita Y. Oleamide derivatives are prototypical anti-metastasis drugs that act by inhibiting Connexin 26. Curr Drug Saf. 2007; 2: 204-11.
40.Czyz J. The stage-specific function of gap junctions during tumourigenesis. Cell Mol Biol Lett. 2008; 13: 92-102.
41.McLachlan E, Shao Q, Laird DW. Connexins and gap junctions in mammary gland development and breast cancer progression. J Membr Biol. 2007; 218: 107-21.
42.Laird DW. Life cycle of connexins in health and disease. Biochem J. 2006; 394: 527-43.
43.Mesnil M, Crespin S, Avanzo JL, Zaidan-Dagli ML. Defective gap junctional intercellular communication in the carcinogenic process. Biochim Biophys Acta. 2005; 1719: 125-45.
44.Jiang JX, Penuela S. Connexin and pannexin channels in cancer. BMC Cell Biol. 2016; 17 Suppl 1: 12.
45.Loewenstein WR, Kanno Y. Intercellular communication and the control of tissue growth: lack of communication between cancer cells. Nature. 1966; 209: 1248-9.
46.Naus CC. Gap junctions and tumour progression. Can J Physiol Pharmacol. 2002; 80: 136-41.
47.Naus CC, Laird DW. Implications and challenges of connexin connections to cancer. Nat Rev Cancer. 2010; 10: 435-41.
48.Avanzo JL, Mesnil M, Hernandez-Blazquez FJ, et al. Increased susceptibility to urethane-induced lung tumors in mice with decreased

expression of connexin43. Carcinogenesis. 2004; 25: 1973-82.
49.King TJ, Lampe PD. The gap junction protein connexin32 is a mouse lung tumor suppressor. Cancer Res. 2004; 64: 7191-6.
50.Zhang A, Hitomi M, Bar-Shain N, et al. Connexin 43 expression is associated with increased malignancy in prostate cancer cell lines and functions to promote migration. Oncotarget. 2015; 6: 11640-51.
51.Penuela S, Bhalla R, Gong XQ, et al. Pannexin 1 and pannexin 3 are glycoproteins that exhibit many distinct characteristics from the connexin family of gap junction proteins. J Cell Sci. 2007; 120: 3772-83.
52.Chekeni FB, Elliott MR, Sandilos JK, et al. Pannexin 1 channels mediate 'find-me' signal release and membrane permeability during apoptosis. Nature. 2010; 467: 863-7.
53.Penuela S, Bhalla R, Nag K, Laird DW. Glycosylation regulates pannexin intermixing and cellular localization. Mol Biol Cell. 2009; 20: 4313-23.
54.Bao L, Locovei S, Dahl G. Pannexin membrane channels are mechanosensitive conduits for ATP. FEBS Lett. 2004; 572: 65-8.
55.Ishikawa M, Iwamoto T, Nakamura T, Doyle A, Fukumoto S, Yamada Y. Pannexin 3 functions as an ER Ca(2+) channel, hemichannel, and gap junction to promote osteoblast differentiation. J Cell Biol. 2011; 193: 1257-74.
56.Iwamoto T, Nakamura T, Doyle A, et al. Pannexin 3 regulates intracellular ATP/cAMP levels and promotes chondrocyte differentiation. J Biol Chem. 2010; 285: 18948-58.
57.Baranova A, Ivanov D, Petrash N, et al. The mammalian pannexin family is homologous to the invertebrate innexin gap junction proteins. Genomics. 2004; 83: 706-16.
58.Uhlen M, Fagerberg L, Hallstrom BM, et al. Proteomics. Tissue-based map of the human proteome. Science. 2015; 347: 1260419.
59.Furlow PW, Zhang S, Soong TD, et al. Mechanosensitive pannexin-1 channels mediate microvascular metastatic cell survival. Nat Cell Biol. 2015; 17: 943-52.
60.Dunn JH, Ellis LZ, Fujita M. Inflammasomes as molecular mediators of inflammation and cancer: potential role in melanoma. Cancer Lett. 2012; 314: 24-33.
61.Schalper KA, Carvajal-Hausdorf D, Oyarzo MP. Possible role of hemichannels in cancer. Front Physiol. 2014; 5: 237.
62.Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity. 2004; 20: 319-25.
63.Gombault A, Baron L, Couillin I. ATP release and purinergic signaling in NLRP3 inflammasome activation. Front Immunol. 2012; 3: 414.
64.Martinon F, Agostini L, Meylan E, Tschopp J. Identification of bacterial muramyl dipeptide as activator of the NALP3/cryopyrin inflammasome. Curr Biol. 2004; 14: 1929-34.
65.Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. Annu Rev Immunol. 2009; 27: 229-65.
66.Martinon F, Tschopp J. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. Cell. 2004; 117: 561-74.
67.Kanneganti TD, Body-Malapel M, Amer A, et al. Critical role for Cryopyrin/Nalp3 in activation of caspase-1 in response to viral infection and double-stranded RNA. J Biol Chem. 2006; 281: 36560-8.
68.Mariathasan S, Weiss DS, Newton K, et al. Cryopyrin activates the inflammasome in response to toxins and ATP. Nature. 2006; 440: 228-32.
69.Chen GY, Nunez G. Inflammasomes in intestinal inflammation and cancer. Gastroenterology. 2011; 141: 1986-99.
70.Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. Nat Rev Immunol. 2013; 13: 397-411.
71.Dupaul-Chicoine J, Arabzadeh A, Dagenais M, et al. The Nlrp3 Inflammasome Suppresses Colorectal Cancer Metastatic Growth in the Liver by Promoting Natural Killer Cell Tumoricidal Activity. Immunity. 2015; 43: 751-63.
72.van Deventer HW, Burgents JE, Wu QP, et al. The inflammasome component NLRP3 impairs antitumor vaccine by enhancing the accumulation of tumor-associated myeloid-derived suppressor cells. Cancer Res. 2010; 70: 10161-9.
73.Chow MT, Tschopp J, Moller A, Smyth MJ. NLRP3 promotes inflammation-induced skin cancer but is dispensable for asbestos-induced mesothelioma. Immunol Cell Biol. 2012; 90: 983-6.
74.Ghiringhelli F, Apetoh L, Tesniere A, et al. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat Med. 2009; 15: 1170-8.
75.Allen IC, TeKippe EM, Woodford RM, et al. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. J Exp Med. 2010; 207: 1045-56.
76.Chen CJ, Shi Y, Hearn A, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. J Clin Invest. 2006; 116: 2262-71.
77.Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006; 440: 237-41.
78.Joosten LA, Netea MG, Mylona E, et al. Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1beta production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis. Arthritis Rheum. 2010; 62: 3237-48.
79.Terkeltaub R, Sundy JS, Schumacher HR, et al. The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. Ann Rheum Dis. 2009; 68: 1613-7.
80.Hellwig-Burgel T, Rutkowski K, Metzen E, Fandrey J, Jelkmann W. Interleukin-1beta and tumor necrosis factor-alpha stimulate DNA binding of hypoxia-inducible factor-1. Blood. 1999; 94: 1561-7.
81.Vakkala M, Kahlos K, Lakari E, Paakko P, Kinnula V, Soini Y. Inducible nitric oxide synthase expression, apoptosis, and angiogenesis in in situ and invasive breast carcinomas. Clin Cancer Res. 2000; 6: 2408-16.
82.Zhang L, Liu J, Wang X, et al. Upregulation of cytoskeleton protein and extracellular matrix protein induced by stromal-derived nitric oxide promotes lung cancer invasion and metastasis. Curr Mol Med. 2014; 14: 762-71.
83.Klotz T, Bloch W, Volberg C, Engelmann U, Addicks K. Selective expression of inducible nitric oxide synthase in human prostate carcinoma. Cancer. 1998; 82: 1897-903.
84.Swana HS, Smith SD, Perrotta PL, Saito N, Wheeler MA, Weiss RM. Inducible nitric oxide synthase with transitional cell carcinoma of the bladder. J Urol. 1999; 161: 630-4.
85.Kojima M, Morisaki T, Tsukahara Y, et al. Nitric oxide synthase expression and nitric oxide production in human colon carcinoma tissue. J Surg Oncol. 1999; 70: 222-9.
86.Singh S, Gupta AK. Nitric oxide: role in tumour biology and iNOS/NO-based anticancer therapies. Cancer Chemother Pharmacol. 2011; 67: 1211-24.

87.Dinarello CA. Why not treat human cancer with interleukin-1 blockade? Cancer Metastasis Rev. 2010; 29: 317-29.
88.Dinarello CA. The paradox of pro-inflammatory cytokines in cancer. Cancer Metastasis Rev. 2006; 25: 307-13.
89.Bhat IA, Naykoo NA, Qasim I, et al. Association of interleukin 1 beta (IL-1beta) polymorphism with mRNA expression and risk of non small cell lung cancer. Meta Gene. 2014; 2: 123-33.
90.Azad N, Rojanasakul Y, Vallyathan V. Inflammation and lung cancer: roles of reactive oxygen/nitrogen species. J Toxicol Environ Health B Crit Rev. 2008; 11: 1-15.
91.Gagne V, Marois L, Levesque JM, et al. Modulation of monosodium urate crystal-induced responses in neutrophils by the myeloid inhibitory C-type lectin-like receptor: potential therapeutic implications. Arthritis Res Ther. 2013; 15: R73.
92.So A. How to regulate neutrophils in gout. Arthritis Res Ther. 2013; 15: 118.
93.Baggiolini M, Walz A, Kunkel SL. Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. J Clin Invest. 1989; 84: 1045-9.
94.Bunger S, Haug U, Kelly M, et al. A novel multiplex-protein array for serum diagnostics of colon cancer: a case-control study. BMC Cancer. 2012; 12: 393.
95.Pengjun Z, Xinyu W, Feng G, et al. Multiplexed cytokine profiling of serum for detection of colorectal cancer. Future Oncol. 2013; 9: 1017-27.
96.Kantola T, Klintrup K, Vayrynen JP, et al. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. Br J Cancer. 2012; 107: 1729-36.
97.Kaminska J, Nowacki MP, Kowalska M, et al. Clinical significance of serum cytokine measurements in untreated colorectal cancer patients: soluble tumor necrosis factor receptor type I--an independent prognostic factor. Tumour Biol. 2005; 26: 186-94.
98.Xie K. Interleukin-8 and human cancer biology. Cytokine Growth Factor Rev. 2001; 12: 375-91.