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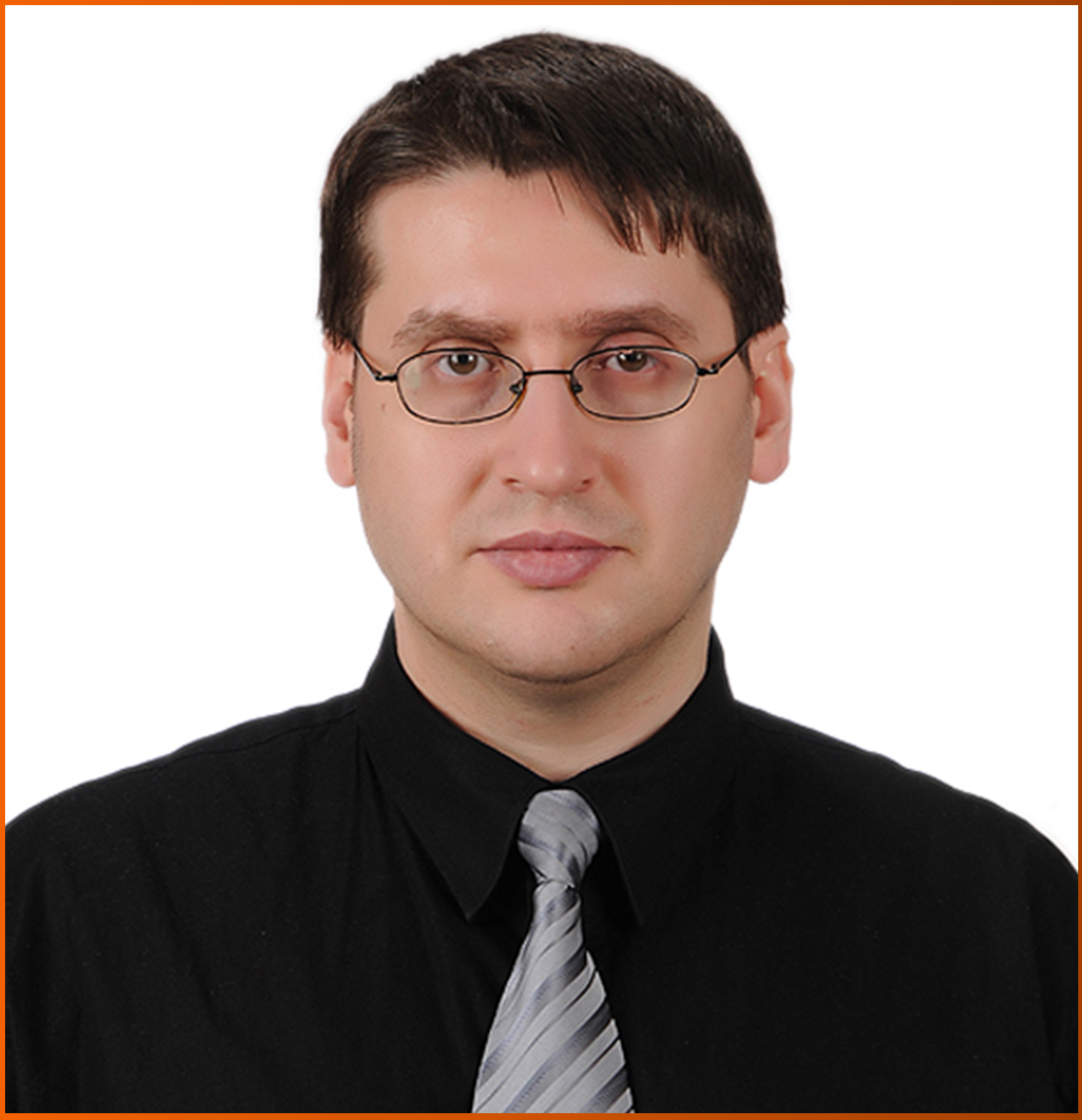

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REVIEW

Neutrophil extracellular traps in gastrointestinal cancer

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Abstract

Gastrointestinal (GI) cancer is a high-risk malignancy and is characterized by high mortality and morbidity worldwide. Neutrophil extracellular traps (NETs), a weblike structure consisting of chromatin DNA with interspersed cytoplasmic and granule proteins, are extruded by activated neutrophils to entrap and kill bacteria and fungi. However, accumulating evidence shows that NETs are related to the progression and metastasis of cancer. In clinical studies, NETs infiltrate primary GI cancer tissues and are even more abundant in metastatic lesions. The quantity of NETs in peripheral blood is revealed to be associated with ascending clinical tumour stages, indicating the role of NETs as a prognostic markers in GI cancer. Moreover, several inhibitors of NETs or NET-related proteins have been discovered and used to exert anti-tumour effects *in vitro* or *in vivo*, suggesting that NETs can be regarded as targets in the treatment of GI cancer. In this review, we will focus on the role of NETs in gastric cancer and colorectal cancer, generalizing their effects on tumour-related thrombosis, invasion and metastasis. Recent reports are also listed to show the latest evidences of how NETs affect GI cancer. Additionally, notwithstanding the scarcity of systematic studies elucidating the underlying mechanisms of the interaction between NETs and cancer cells, we highlight the potential importance of NETs as biomarkers and anti-tumour therapeutic targets.

Key Words: Neutrophil extracellular traps; Gastric cancer; Colorectal cancer; Biomarkers; Therapeutic targets

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Core Tip: Neutrophil extracellular traps (NETs) have been reported to participate in progression and metastasis in gastrointestinal (GI) cancer. Recent reports demonstrate that NET formation is enhanced in GI cancer patients as well as some mouse models and that elevated levels of NETs indicate an adverse outcome in patients. Furthermore, NETs can trap disseminated cancer cells and assist the formation of metastatic lesions although the underlying mechanisms remain vague. More studies are needed before NETs can be used as reliable biomarkers and therapeutic targets in GI cancer.

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INTRODUCTION

According to cancer statistics, gastric cancer (GC) ranks third globally in terms of mortality, while colorectal cancer (CRC) is the second leading cause of cancer-related death. Both constitute a major cause of cancer-related death worldwide[1,2]. Despite advances in the techniques applied for cancer treatment, surgical resection accompanied by adjuvant therapy (chemotherapy, radiotherapy and molecular targeted therapies) remains the primary approach[3]. However, the efficacy of aforementioned treatment is related to tumour heterogeneity in patients[4]. Once the tumour progresses and spreads to distant organs (*e.g.*, liver and lung), neither conventional surgery nor targeted therapies can reverse the dismal outcomes[5]. Therefore, it is of high importance in all future studies to understand the mechanisms of deterioration of GI cancer, by measuring not only the tumour itself, but also the surrounding cells that can be modified by the tumour to generate a supportive microenvironment; these cells include macrophages (tumour-associated macrophages), fibroblasts (cancer-associated fibroblasts) and neutrophils (tumour-associated neutrophils)[6,7].

Neutrophil extracellular traps (NETs) are extruded by activated neutrophils into the extracellular environment and have three-dimensional lattices, which are composed of decondensed chromatin with interspersed proteins such as neutrophil elastase (NE), cathepsin G, myeloperoxidase (MPO), histones and some other antimicrobial peptides [8,9]. NETs were originally discovered to ensnare and kill extracellular bacteria and fungi and may act as a physical barrier to impede the dissemination of microbes[10]. However, recent studies have revealed that NETs, if dysregulated, can contribute to the development or progression of some inflammatory or immune-related diseases[11,12], such as atherosclerosis[13], systemic lupus erythematosus (SLE)[14], diabetes[15], vasculitis[16], wound healing[17] and coronavirus disease 2019 (COVID-19)[18]. COVID-19 is still spreading worldwide, and clinical evidence shows that increased NET formation after the COVID-19 infection can be a potential biomarker for disease severity[19]; thus, targeting NETs may alleviate the condition of patients[20]. More work is needed before NETs can be used as reliable biomarkers in these diseases. In addition to the roles of NETs mentioned before, studies have expanded their biological scope and suggest that elevated numbers of neutrophils and levels of NETs in peripheral circulation are a hallmark of cancer[21]. Recently, NETs have been suggested to participate in the biological process of cancer[22-24]. Several studies have shown that NETs can cause hypercoagulability[25], accumulate in peripheral blood vessels and impair organ function[26], promote cancer development and metastasis[27-30], sequester circulating tumour cells[31,32], and even stimulate dormant cancer cells[33]. Therefore, more work needs to be done to elucidate the mechanism between NETs and cancer.

In this review, we will discuss the role of NETs in GC and CRC according to the latest findings and consider their potential of NETs as biomarkers and therapeutic targets.

NETS

The formation of NETs, known as NETosis, was first observed by Takei *et al*[34] *via* stimulation with phorbol-12-myristate-13-acetate (PMA) and is regarded as a novel form of neutrophil death that is different from apoptosis and necrosis. The antibacterial role of NETs was confirmed in 2004 and is dependent on the web-like structure [10]. The core scaffold of NETs is the nuclear DNA extruded from neutrophils and that forms a three-dimensional meshwork with a number of interspersed specific cytoplasmic and granular proteins[35]. Notwithstanding the lack of mechanistic or interventional studies investigating NET formation in peripheral circulation, initial studies suggest that NETs are released by dying neutrophils. This phenomenon of NET formation can be mainly described by at least two mechanisms. One mechanism requires the lytic suicide of neutrophils, while the other mechanism is independent of this process[36,37]. Neubert *et al*[38] demonstrated that entropic chromatin swelling is the major physical driving force of NETosis. In addition, other myeloid cells, such as human blood monocytes[39], mast cells[40] and eosinophils[41], have been discovered to release DNA networks. However, neutrophils seem to remain the main source of these networks because of their high efficiency of secretion.

The functions of NETs in defending against infection depend on the composition of the network, including the DNA itself, which is a chelator of divalent cations that possesses antibacterial ability. The citrullination of histones loosens their grip on DNA and provides a chance for interaction between DNA and bacteria[42]. Moreover, highly toxic modified histones, which constitute the major part of NET-associated proteins, are also mediators of bactericide[43]. Moreover, NE synergizes with MPO to assist the formation and antibacterial role of NETs[44]. More generally, NETs prevent dissemination of infection by entrapping microbes and facilitate their killing by bactericidal proteins which have been shown to be involved in both direct and indirect mechanisms. In addition, NETs are revealed to be vital factors in non-infectious diseases. Hakkim *et al*[45] suggested that the persistence of NETs exacerbates the autoimmune response and forms a vicious cycle in SLE. Similarly, studies on diabetes [15], vasculitis[16], wound healing[17] and COVID-19[18-20] have described the pathophysiological role of NETs.

Recently, an emerging role of NETs in promoting cancer progression has been described. Solid tumours are prone to generating a leukemoid reaction and pre-educate neutrophils to form extracellular DNA traps, and intratumoural NET formation is associated with thrombosis[46]. The accumulation of tumour-induced NETs in the peripheral circulation drives the systemic inflammation and vascular dysfunction in mice with cancer[26]. Leal *et al*[47] indicates that NETs serve as scaffolds and collaborate with tumour-derived procoagulant exosomes in the establishment of a prothrombotic phenotype in cancer. CXCL8 (interleukin-8, IL8) is a chemokine that can be produced by tumour cells and its role in promoting angiogenesis in cancer has been well discussed[48]. Furthermore, the presence of IL8 activates the extrusion of NETs with potential involvement in cancer progression and promotes cancer cell metastasis partially through AKT and STAT3 signalling pathways[49,50]. NETs produced by tumour-infiltrating neutrophils mediate the crosstalk between the tumour microenvironment and deterioration by regulating the HMGB1/RAGE/IL8 axis[51]. IL17 is a cytokine described as a protumourigenic factor involved in the initiation and development of cancer[52]. A recent study demonstrated that IL17 can induce NETosis through epithelial cell signalling to favour tumour growth[53]. Rocks *et al*[54] associated NETs with cancer cells and confirmed that the release of NETs favour tumour cell dissemination and colonization in organs.

Since the discovery of NETs, the role of neutrophils and NETs has attracted increasing attentions. Additional studies have reported on numerous stimuli that affect NET formation *in vitro* and *in vivo*. PMA, a potent artificial activator of the neutrophil respiratory burst, has been broadly applied to identify the mechanism of NETosis. Cytokines, such as the aforementioned IL8, IL17 and tumour necrosis factor alpha[55], have been investigated with respect to their role in expediting NET formation. Nicotine, a major addictive component of tobacco, is reported to induce NETosis in a dose-dependent manner, implying potential threats to human health[56]. Moreover, sulfasalazine, a drug used to treat inflammatory bowel disease and rheumatoid arthritis, has been found to significantly promote NETosis by accelerating lipid oxidation [57]. Most recently, Yasuda *et al*[58] established the relationship between NETosis and epigenetics and demonstrated that DNA demethylation enhances spontaneous NET formation by reinforcing PAD4 expression and histone citrullination.

NETS IN GC

GC is the fifth most common cancer and ranks third in terms of mortality worldwide. Several studies have tried to confirm the characteristics of NETs in GC and clarify the underlying mechanisms *in vitro* and *in vivo* (Table 1).

Notwithstanding advances in diagnosis and therapy, recurrence and metastasis are still common as a result of its high molecular and phenotypic heterogeneity[59], which contributes to a coagulable state that causes the proliferation and invasion of GC cells [60-63]. In GC patients, NET formation is significantly upregulated and its increased level is consistent with advanced TNM stage. Moreover, a procoagulant role of NETs in GC has been confirmed. When NETosis is inhibited by DNase I, the levels of TAT and D-dimers are downregulated. Furthermore, NETs obtained from GC patients can also stimulate control plasma to generate thrombin and fibrin[64].

A common target of metastatic gastrointestinal cancer is the peritoneal cavity[65]. The invention of heated intraperitoneal chemotherapy[66] and postoperative chemotherapy[67] has indeed reduced the rate of peritoneal recurrence and metastasis. However, limitations still exist with regard to the benefit of these treatments, and severe general toxicity has always been an unavoidable side effect. To elucidate the underlying mechanisms, Kanamaru *et al*[68,69] collected the peritoneal lavages from GC patients before and after radical surgery. Then NET formation emerged after short term culture of purified low-density neutrophils (LDNs) separated from the lavages fluids. Moreover, the majority of NET-like structures were discovered on the surface of omental tissue. In a *in vivo* study, GC cells lines such as MKN45, OCUM-1 and NUGC-4 were found attached to the NETs and remained healthy; this interaction was entirely prevented upon treatment with DNase I, which can degrade NETs.

Notwithstanding the advances of therapeutic strategies in GC, surgical resection remains the mainstay treatment. Therefore, the subsequent surgical stress, which suppresses immunity, constitutes one of the key factors that influence the prognosis of GC patients[70,71]. The percentage of LDNs in the peripheral circulation of GC patients who underwent abdominal surgery was elevated and *in vitro* studies observed the adhesion of cancer cells to NET structure, suggesting that partial adverse effects of surgical stress may be explained by the formation of NETs[72].

According to a pulmonary metastasis model of GC, accumulation of neutrophils in the adjacent vascular vessels has been found during the colonization of GC cells. Extracts from the root of *Salvia miltiorrhiza* (*Danshen*)[73], a medicinal plant used for cancer therapy, have been observed to prevent neutrophil trafficking to the metastatic sites and obstruct the formation of NETs *via* inhibitory activities on MPO and NADPH oxidase (NOX)[74]. A recent study has proposed that obstruction of NETosis by Cl-amidine or DNase I significantly suppresses the progression of GC cells by regulating the expression of apoptosis-associated genes, among which Bcl-2[75] levels were downregulated and the expression of Bax[76] and NF-κB p65[77] increased significantly[78].

NETS IN CRC

CRC is the third most frequent malignancy and second leading cause of cancer-related mortality worldwide. To date, metastasis and cancer-associated thrombosis are still the main causes of death in CRC patients. To address this issue, much work has been done or is currently in progress; recently, more attention has been drawn to the establishment of tumour microenvironment. Of note, recent accumulating evidence has shown that NETs may play a pivotal role in the progression of CRC (Table 2).

CRC patients are at high risk of venous thrombosis as a result of hypercoagulable state and the levels of NETs in the peripheral blood are positively related to cancer progression. A comparison between 60 newly diagnosed CRC patients and 20 healthy controls revealed that neutrophils in CRC patients can release more NETs, and this tendency parallels increased TAT levels and fibrin formation, which is indicative of a hypercoagulable state[79]. Thus, a vicious cycle can be established between activated platelets and neutrophils. Additionally, *in vitro* studies show that NETs can convert endothelial cells to a procoagulant phenotype[80]. Another study observed that NETs were concentrated in the centre of CRC tissues and reduced gradually towards adjacent normal tissues, and this characteristic could help surgeons determine a better surgical area through pathological examination of the tumour margins. Furthermore, tissue factor, a stimulus of coagulation and a pro-angiogenic factor, was discovered in NETs from the primary tumour and metastatic lymph nodes[81]. Altogether, the

Table 1 Role of neutrophil extracellular traps in gastric cancer

Ref.	Cell lines	Model (*in vitro*, *in vivo*, human)	Conclusion
Yang *et al*[64], 2015	-	Human	NETs contribute to the hypercoagulable state in GC patients with stage III/IV
Kanamaru *et al* [68], 2018	MKN45, NUGC-4, OCUM-1	*In vitro*, *in vivo*	NETs on peritoneal surface assist the clustering and growth of GC tumor cells disseminated in abdomen
Tao *et al*[74], 2018	BGC-823	*In vitro*, *in vivo*	NET formation is inhibited by Sal B and DHT I at the earlier stage
Kumagai *et al* [72], 2020	MKN45, NUGC-4, OCUM-1	*In vitro*, human	NETs formation is enhanced under surgical stress and can effectively trap circulating tumor cells
Li *et al*[78], 2020	BGC-823, SGC7901, MKN28	*In vitro*, human	NETs destruction promotes the apoptosis and inhibits the invasion of gastric cancer cells by regulating the expression of Bcl-2, Bax and NF-κB
Zhang *et al*[94], 2020	-	Human	NETs have novel diagnostic, therapeutic predictive, and prognostic value in GC patients

NETs: Neutrophil extracellular traps; GC: Gastric cancer.

Table 2 Role of neutrophil extracellular traps in colorectal cancer

Ref.	Cell lines	Model (*in vitro*, *in vivo*, human)	Conclusion
Arelaki *et al* [81], 2016	Caco-2	*In vitro*, human	NETs concentration is gradually reduced from the tumor mass to the distal margin
Tohme *et al* [83], 2016	MC38	*In vitro*, human	Surgical stress and intratumoral hypoxia induce NETs formation and NETs can trigger HMGB1 release and activate TLR9-dependent pathways to promote adhesion, proliferation, migration, and invasion in CRC
Richardson *et al* [84], 2017	-	Human	NET production in the later postoperative period appears to coincide with surgical recovery
Arelaki *et al* [88], 2018		Human	PolyP is present in human colon cancer and increase NETosis
Rayes *et al*[82], 2019	MC38, H59	*In vitro*, *in vivo*, human	Circulating NET levels are elevated in advanced CRC and blocking NETosis significantly inhibits spontaneous metastasis to the lung and liver
Yazdani *et al* [89], 2019	MC38, HCT116, Hepa 1-6, Huh7	*In vitro*, *in vivo*, human	NETs facilitate the growth of stressed cancer cells by altering their bioenergetics
Zhang *et al*[80], 2019	HUVECs	*In vitro*, human	NETs are involved in the progression of CRC and act as potential agonists in CRC-related hypercoagulability
Rayes *et al* [113], 2020	HT-29, MC38, A549	*In vitro*, *in vivo*, human	NET-associated CEACAM1 acts as a putative therapeutic target to prevent the metastatic progression of colon carcinoma
Shang *et al*[92], 2020	DKs-8, DKO-1, PMN	*In vitro*, *in vivo*, human	Exosomes may transfer mutant KRAS to recipient cells and trigger increases in IL-8 production, neutrophil recruitment and formation of NETs, eventually leading to the deterioration of CRC
Xia *et al*[105], 2020	MC38, HepG2	*In vitro*, *in vivo*	AAV-mediated DNase I liver gene transfer is a safe and effective modality to inhibit metastasis and represents a novel therapeutic strategy for CRC
Yang *et al*[91], 2020	HT29, MC38	*In vitro*, *in vivo*, human	A novel positive feedback between elevated tumorous IL-8 and NETs can promote CRC liver metastasis
Yang *et al*[93], 2020	HCT116, MDA-MB-231, MCF-7, 4T1, HEK293T, HeLa, E0771	*In vitro*, *in vivo*, human	CCDC25 mediates NET-dependent metastasis and is suggested to be a therapeutic target for the prevention of cancer metastasis

NETs: Neutrophil extracellular traps; CRC: Colorectal cancer; AAV: Adeno-associated virus.

presence of NETs contributes to thrombosis in CRC.

By analysing large-scale human data, Rayes *et al*[82] demonstrated that NETs can not only bind tumour cells but also promote metastasis. In addition, established preclinical models of gastrointestinal cancer revealed that tumours induce neutrophils to extrude NETs into the extracellular environment in the absence of surgical stress. Furthermore, NET formation could promote CRC metastasis after surgical stress[83,

84]. In a cohort study, increased postoperative NET formation was associated with disease-free survival in patients undergoing hepatic surgical resection, and the mouse model of surgical stress has obtained similar results. Further studies demonstrated that the hypoxic environment in solid tumours provides a favourable condition for NETosis and that NETs could in turn promote CRC progression by releasing HMGB1 [85], a DNA-binding protein that participates in the activation of TLR9[86]. Additionally, the protumourigenic effects of NETs are abolished by DNase and PAD4 inhibition[83]. Another clinical trial suggested that increased preoperative NETosis is related to an increased hospital stay and complications of CRC patients who undergo colorectal resection, suggesting a promising therapeutic benefit of surgery focused on the relationship between CRC and NETs[84].

In malignant and premalignant colon tissues, CD68+ polyP-expressing cells and NETosis were detected, suggesting a possible interaction between them in the tumour microenvironment. Further investigation indicates that polyP[87], which is secreted by activated platelets and could induce inflammation and thrombosis in CRC, may promote the formation of NETs[88]. A PAD4-KO mouse model, which is genetically incapable of NETosis, showed that inhibition of NETs halted CRC growth through its negative regulation of mitochondrial biogenesis-associated genes. Further studies show that CRC cells subjected to hypoxia have upregulated expression of HMGB1 [85], which acts as an inducer of NETosis, and NE released from NETs could assist tumour proliferation as a result of inducing mitochondrial biogenesis by activating the TLR4-p38-PGC1α pathway in CRC[89].

In CRC, IL8 has been reported to participate in growth, angiogenesis and metastasis [90]. High expression of IL8 also implicates adverse survival in patients. A recent study explains a promotional role of IL8 in the formation of NETs. *In vitro* adhesion system, CRC cells such as HT29 and MC38 cells are more prone to be entrapped into NETs than neutrophil monolayers, giving the chance for disseminated CRC cells to form micrometastases in the liver; this process can be enhanced by overexpression of IL8[91]. Another study focuses on exosomes secreted by CRC cells. The authors showed that exosomes derived from KRAS mutant cells could transfer mutant KRAS to receptors and upregulate IL8 Levels, eventually activating neutrophils to form NETs and leading to enhanced proliferation and invasion of cancer cells[92].

The aforementioned studies have highlighted an interaction between CRC cells and NETs, suggesting that NET formation is enhanced in tumours and that the increase in NETs can promote the progression and metastasis of CRC. Although several pathways have been described, the detailed mechanisms of how NETs interact with and boost the metastasis of CRC remain elusive. Most recently, a remarkable discovery not only precisely illustrates the underlying mechanism between CRC cells and NETs but also partially explains why CRC cells have a tendency to disseminate into the liver. Yang *et al*[93] investigated several metastatic lesions in the clinic and discovered the most abundant NET infiltration in liver metastases and the formation of NETs began before the appearance of the metastases. According to a pull-down assay, CCDC25, a potential cell-surface DNA receptor, was identified on the cytoplasmic membrane of cancer cells. Furthermore, amino acids 21-25 at the extracellular N-terminus of CCDC25 were found to be the binding site of NET-DNA. Further immunoprecipitation assays indicated that the intracellular C-terminus of CCDC25 binds integrin-linked kinase and that this interaction can be stimulated by NET-DNA, eventually inducing liver metastases of CRC cells *via* initiating the β-parvin-RACI-CDC42 cascade.

NETS AS POTENTIAL BIOMARKERS AND THERAPEUTIC TARGETS

An increasing number of investigations have suggested a protumourigenic role of NETs in providing a microenvironment favouring interactions and promoting cancer proliferation, thrombosis and metastasis in GI cancers. This has led to the question of whether NETs can act as potential biomarkers and therapeutic targets.

Zhang *et al*[94] compared the levels of NETs in different patient populations, suggesting that NETs, as a diagnostic biomarker, have better value than carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 in GC. Additionally, NET formation is associated with tumour stage, poor overall survival and poor recurrence-free survival. Moreover, tumour-infiltrating NETs has been demonstrated to be an independent prognostic biomarker according to the assessment of clinical outcomes of cancer patients[95-97]. Considering the potential diagnostic significance of NETs, conventional histological staining is ineffective for their detection in tissue. To solve

this problem, a protocol has been created to detect NETs in paraffin-embedded tissue [98]. Additionally, machine learning is described as a useful tool to quantitate NETosis [99]. Citrullinated histone H3, a central marker of NETs, is elevated in blood and regarded as a potential diagnostic and prognostic serum marker to predict the risk of venous thromboembolism and mortality in patients with advanced cancer[100-102]. A CitH3DNA binding assay has also been developed to quantify NET formation[103].

Taking into account the confirmed role of NETs in promoting the progression and metastasis of GI cancer cells, disruption of NETosis can be a possible new therapeutic strategy and the identification of NETosis inhibitors is of high interest. DNase I can degrade the DNA backbone of NETs and abrogate the protumourigenic ability of NETs in several aforementioned animal models. Moreover, DNase I has been safely used in cystic fibrosis and SLE patients[104], implying that DNase I can act as a promising candidate for the treatment of GI cancer patients. In a mouse model of CRC liver metastasis, an adeno-associated virus gene therapy vector was created to specifically express DNase I in the liver, inducing an inhibition of liver metastasis[105]. However, it is worth noting that everything is a double-edged sword. Inappropriate use of DNase I may lead to a systemic inflammatory response in patients[106]. Owing to the critical role of NE and PAD4 in the process of NETosis, NE inhibitors or PAD4-inhibitors are also commonly used to prevent the release of NETs. Nanoparticle-mediated delivery of NE inhibitors has been suggested as a feasible approach to decrease NETosis[107]. In addition, NOX inhibitors[108], MPO inhibitors[109] and RAF inhibitors[110] have been reported to arrest the inception of NETosis. Recently, a group of tetrahydroisoquinolines was found to be a novel class of NET formation inhibitors, but their underlying mechanism remains to be determined[111]. A drug screening of 126 compounds shows that appropriate use of anthracyclines (drugs used for cancer treatment) together with dexrazoxane could be a promising therapeutic candidate for suppressing NETosis without cytotoxicity against healthy neutrophils [112]. NET-associated CEA cell adhesion molecule 1 (CEACAM1) was identified by Rayes *et al*[113] Knockdown of CEACAM1 on NETs abrogates the adhesion between NETs and colon cancer cells, thus indicating a potential therapeutic therapy or preventing liver metastases. A novel study revealed that PKCα, a lamin kinase that mediates the phosphorylation of lamin B, contributes to the formation of NETs; hence, blocking PKCα provides a new perspective towards treating NET-associated cancer progression[114]. Since the application of 5-fluorouracil (5FU) has been shown to trigger the formation of NETs in the blood of cancer patients, Amph-PVP self-assembled nanoparticles are proposed as an efficient delivery system for 5FU to avoid the generation of NETs, partially improving the anticancer effect and reducing the risk of long-term metastasis[115]. The previously mentioned studies mainly focus on the inhibition of NETosis or the proteins assembled in NETs. Unusually, Cao and King [116] proposed that NETs per se can be utilized as an anti-tumour drug delivery vehicle. By re-engineering neutrophils, supercharged eGFP-TRAIL, an apoptosis-inducing chimeric protein, is expressed on NETs to entrap and kill tumour cells.

CONCLUSION

NETs, initially identified as a host defense system designed to trap and kill bacteria, have now been suggested to play an important tumorigenic role in many cancers. Accumulating evidence has shown that NETs are involved in GI cancers, including GC and CRC. As mentioned above, NET infiltration in primary tumour tissues implies a poor outcome in GI cancer patients, indicating that a rapid intraoperative histopathological examination of NETs in the resected tissue margins may help determine the range of surgical resection. Moreover, several cytokines and genetic mutations trigger the formation of NETs and NETs per se can promote the progression of cancer partially by initiating downstream signalling pathways. On the other hand, the fact that NETs can entrap disseminated cancer cells, combined with the situation that an abundance of NET infiltration in the liver is formed before metastases can be detected, increases the likelihood of liver metastasis and explains the high incidence of liver metastasis in patients with GI cancer.

Further studies are needed to elucidate the detailed underlying mechanism of the interaction between NETs and GI cancer. Clarifying the roles of NETs in cancer could open a new door in the design and development of therapeutic approaches. Transforming inhibitors of NETs into drugs that can be safely used in GI cancer patients or utilizing NETosis as a drug delivery system may evolve into promising anti-tumour therapies.

REFERENCES

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]

2 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

3 **Saad ED**, Buyse M. Statistical aspects in adjuvant and neoadjuvant trials for gastrointestinal cancer in 2020: focus on time-to-event endpoints. *Curr Opin Oncol* 2020; **32**: 384-390 [PMID: 32541329 DOI: 10.1097/CCO.0000000000000636]

4 **Parikh AR**, Leshchiner I, Elagina L, Goyal L, Levovitz C, Siravegna G, Livitz D, Rhrissorrakrai K, Martin EE, Van Seventer EE, Hanna M, Slowik K, Utro F, Pinto CJ, Wong A, Danysh BP, de la Cruz FF, Fetter IJ, Nadres B, Shahzade HA, Allen JN, Blaszkowsky LS, Clark JW, Giantonio B, Murphy JE, Nipp RD, Roeland E, Ryan DP, Weekes CD, Kwak EL, Faris JE, Wo JY, Aguet F, Dey-Guha I, Hazar-Rethinam M, Dias-Santagata D, Ting DT, Zhu AX, Hong TS, Golub TR, Iafrate AJ, Adalsteinsson VA, Bardelli A, Parida L, Juric D, Getz G, Corcoran RB. Liquid *vs* tissue biopsy for detecting acquired resistance and tumour heterogeneity in gastrointestinal cancers. *Nat Med* 2019; **25**: 1415-1421 [PMID: 31501609 DOI: 10.1038/s41591-019-0561-9]

5 **Zhao Y**, Li J, Li D, Wang Z, Zhao J, Wu X, Sun Q, Lin PP, Plum P, Damanakis A, Gebauer F, Zhou M, Zhang Z, Schlösser H, Jauch KW, Nelson PJ, Bruns CJ. Tumour biology and multidisciplinary strategies of oligometastasis in gastrointestinal cancers. *Semin Cancer Biol* 2020; **60**: 334-343 [PMID: 31445220 DOI: 10.1016/j.semcancer.2019.08.026]

6 **Quail DF**, Joyce JA. Microenvironmental regulation of tumour progression and metastasis. *Nat Med* 2013; **19**: 1423-1437 [PMID: 24202395 DOI: 10.1038/nm.3394]

7 **Galdiero MR**, Bianchi P, Grizzi F, Di Caro G, Basso G, Ponzetta A, Bonavita E, Barbagallo M, Tartari S, Polentarutti N, Malesci A, Marone G, Roncalli M, Laghi L, Garlanda C, Mantovani A, Jaillon S. Occurrence and significance of tumour-associated neutrophils in patients with colorectal cancer. *Int J Cancer* 2016; **139**: 446-456 [PMID: 26939802 DOI: 10.1002/ijc.30076]

8 **Ravindran M**, Khan MA, Palaniyar N. Neutrophil Extracellular Trap Formation: Physiology, Pathology, and Pharmacology. *Biomolecules* 2019; **9**: 365 [PMID: 31416173 DOI: 10.3390/biom9080365]

9 **Dąbrowska D**, Jabłońska E, Garley M, Ratajczak-Wrona W, Iwaniuk A. New Aspects of the Biology of Neutrophil Extracellular Traps. *Scand J Immunol* 2016; **84**: 317-322 [PMID: 27667737 DOI: 10.1111/sji.12494]

10 **Brinkmann V**, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A. Neutrophil extracellular traps kill bacteria. *Science* 2004; **303**: 1532-1535 [PMID: 15001782 DOI: 10.1126/science.1092385]

11 **Papayannopoulos V**. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol* 2018; **18**: 134-147 [PMID: 28990587 DOI: 10.1038/nri.2017.105]

12 **Bonaventura A**, Liberale L, Carbone F, Vecchié A, Diaz-Cañestro C, Camici GG, Montecucco F, Dallegri F. The Pathophysiological Role of Neutrophil Extracellular Traps in Inflammatory Diseases. *Thromb Haemost* 2018; **118**: 6-27 [PMID: 29304522 DOI: 10.1160/TH17-09-0630]

13 **Döring Y**, Soehnlein O, Weber C. Neutrophil Extracellular Traps in Atherosclerosis and Atherothrombosis. *Circ Res* 2017; **120**: 736-743 [PMID: 28209798 DOI: 10.1161/CIRCRESAHA.116.309692]

14 **O'Neil LJ**, Kaplan MJ, Carmona-Rivera C. The Role of Neutrophils and Neutrophil Extracellular Traps in Vascular Damage in Systemic Lupus Erythematosus. *J Clin Med* 2019; **8**: 1325 [PMID: 31466329 DOI: 10.3390/jcm8091325]

15 **Bryk AH**, Prior SM, Plens K, Konieczynska M, Hohendorff J, Malecki MT, Butenas S, Undas A. Predictors of neutrophil extracellular traps markers in type 2 diabetes mellitus: associations with a prothrombotic state and hypofibrinolysis. *Cardiovasc Diabetol* 2019; **18**: 49 [PMID: 30992036 DOI: 10.1186/s12933-019-0850-0]

16 **Söderberg D**, Segelmark M. Neutrophil extracellular traps in vasculitis, friend or foe? *Curr Opin Rheumatol* 2018; **30**: 16-23 [PMID: 28957962 DOI: 10.1097/BOR.0000000000000450]

17 **Kaur T**, Dumoga S, Koul V, Singh N. Modulating neutrophil extracellular traps for wound healing. *Biomater Sci* 2020; **8**: 3212-3223 [PMID: 32374321 DOI: 10.1039/d0bm00355g]

18 **Blasco A**, Coronado MJ, Hernández-Terciado F, Martín P, Royuela A, Ramil E, García D, Goicolea J, Del Trigo M, Ortega J, Escudier JM, Silva L, Bellas C. Assessment of Neutrophil Extracellular Traps in Coronary Thrombus of a Case Series of Patients With COVID-19 and Myocardial Infarction. *JAMA Cardiol* 2020; **6**: 1-6 [PMID: 33372956 DOI: 10.1001/jamacardio.2020.7308]

19 **Middleton EA**, He XY, Denorme F, Campbell RA, Ng D, Salvatore SP, Mostyka M, Baxter-Stoltzfus A, Borczuk AC, Loda M, Cody MJ, Manne BK, Portier I, Harris ES, Petrey AC, Beswick EJ, Caulin AF, Iovino A, Abegglen LM, Weyrich AS, Rondina MT, Egeblad M, Schiffman JD, Yost CC. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood* 2020; **136**: 1169-1179 [PMID: 32597954 DOI: 10.1182/blood.2020007008]

20 **Barnes BJ**, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, Daßler-Plenker J, Guerci P, Huynh C, Knight JS, Loda M, Looney MR, McAllister F, Rayes R, Renaud S, Rousseau S, Salvatore S, Schwartz RE, Spicer JD, Yost CC, Weber A, Zuo Y, Egeblad M. Targeting

potential drivers of COVID-19: Neutrophil extracellular traps. *J Exp Med* 2020; **217**: e20200652 [PMID: 32302401 DOI: 10.1084/jem.20200652]

21 **Teramukai S**, Kitano T, Kishida Y, Kawahara M, Kubota K, Komuta K, Minato K, Mio T, Fujita Y, Yonei T, Nakano K, Tsuboi M, Shibata K, Furuse K, Fukushima M. Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: an analysis of Japan Multinational Trial Organisation LC00-03. *Eur J Cancer* 2009; **45**: 1950-1958 [PMID: 19231158 DOI: 10.1016/j.ejca.2009.01.023]

22 **Jung HS**, Gu J, Kim JE, Nam Y, Song JW, Kim HK. Cancer cell-induced neutrophil extracellular traps promote both hypercoagulability and cancer progression. *PLoS One* 2019; **14**: e0216055 [PMID: 31034495 DOI: 10.1371/journal.pone.0216055]

23 **Park J**, Wysocki RW, Amoozgar Z, Maiorino L, Fein MR, Jorns J, Schott AF, Kinugasa-Katayama Y, Lee Y, Won NH, Nakasone ES, Hearn SA, Küttner V, Qiu J, Almeida AS, Perurena N, Kessenbrock K, Goldberg MS, Egeblad M. Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps. *Sci Transl Med* 2016; **8**: 361ra138 [PMID: 27798263 DOI: 10.1126/scitranslmed.aag1711]

24 **Lerman I**, Hammes SR. Neutrophil elastase in the tumour microenvironment. *Steroids* 2018; **133**: 96-101 [PMID: 29155217 DOI: 10.1016/j.steroids.2017.11.006]

25 **Boone BA**, Murthy P, Miller-Ocuin J, Doerfler WR, Ellis JT, Liang X, Ross MA, Wallace CT, Sperry JL, Lotze MT, Neal MD, Zeh HJ 3rd. Chloroquine reduces hypercoagulability in pancreatic cancer through inhibition of neutrophil extracellular traps. *BMC Cancer* 2018; **18**: 678 [PMID: 29929491 DOI: 10.1186/s12885-018-4584-2]

26 **Cedervall J**, Zhang Y, Huang H, Zhang L, Femel J, Dimberg A, Olsson AK. Neutrophil Extracellular Traps Accumulate in Peripheral Blood Vessels and Compromise Organ Function in Tumour-Bearing Animals. *Cancer Res* 2015; **75**: 2653-2662 [PMID: 26071254 DOI: 10.1158/0008-5472.CAN-14-3299]

27 **Takesue S**, Ohuchida K, Shinkawa T, Otsubo Y, Matsumoto S, Sagara A, Yonenaga A, Ando Y, Kibe S, Nakayama H, Iwamoto C, Shindo K, Moriyama T, Nakata K, Miyasaka Y, Ohtsuka T, Toma H, Tominaga Y, Mizumoto K, Hashizume M, Nakamura M. Neutrophil extracellular traps promote liver micrometastasis in pancreatic ductal adenocarcinoma *via* the activation of cancerassociated fibroblasts. *Int J Oncol* 2020; **56**: 596-605 [PMID: 31894273 DOI: 10.3892/ijo.2019.4951]

28 **van der Windt DJ**, Sud V, Zhang H, Varley PR, Goswami J, Yazdani HO, Tohme S, Loughran P, O'Doherty RM, Minervini MI, Huang H, Simmons RL, Tsung A. Neutrophil extracellular traps promote inflammation and development of hepatocellular carcinoma in nonalcoholic steatohepatitis. *Hepatology* 2018; **68**: 1347-1360 [PMID: 29631332 DOI: 10.1002/hep.29914]

29 **Demers M**, Wong SL, Martinod K, Gallant M, Cabral JE, Wang Y, Wagner DD. Priming of neutrophils toward NETosis promotes tumour growth. *Oncoimmunology* 2016; **5**: e1134073 [PMID: 27467952 DOI: 10.1080/2162402X.2015.1134073]

30 **Kajioka H**, Kagawa S, Ito A, Yoshimoto M, Sakamoto S, Kikuchi S, Kuroda S, Yoshida R, Umeda Y, Noma K, Tazawa H, Fujiwara T. Targeting neutrophil extracellular traps with thrombomodulin prevents pancreatic cancer metastasis. *Cancer Lett* 2021; **497**: 1-13 [PMID: 33065249 DOI: 10.1016/j.canlet.2020.10.015]

31 **Cools-Lartigue J**, Spicer J, McDonald B, Gowing S, Chow S, Giannias B, Bourdeau F, Kubes P, Ferri L. Neutrophil extracellular traps sequester circulating tumour cells and promote metastasis. *J Clin Invest* 2013; **13**: 3446-3458 [PMID: 23863628 DOI: 10.1172/JCI67484]

32 **Najmeh S**, Cools-Lartigue J, Rayes RF, Gowing S, Vourtzoumis P, Bourdeau F, Giannias B, Berube J, Rousseau S, Ferri LE, Spicer JD. Neutrophil extracellular traps sequester circulating tumour cells *via* β1-integrin mediated interactions. *Int J Cancer* 2017; **140**: 2321-2330 [PMID: 28177522 DOI: 10.1002/ijc.30635]

33 **Albrengues J**, Shields MA, Ng D, Park CG, Ambrico A, Poindexter ME, Upadhyay P, Uyeminami DL, Pommier A, Küttner V, Bružas E, Maiorino L, Bautista C, Carmona EM, Gimotty PA, Fearon DT, Chang K, Lyons SK, Pinkerton KE, Trotman LC, Goldberg MS, Yeh JT, Egeblad M. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science* 2018; **361** [PMID: 30262472 DOI: 10.1126/science.aao4227]

34 **Takei H**, Araki A, Watanabe H, Ichinose A, Sendo F. Rapid killing of human neutrophils by the potent activator phorbol 12-myristate 13-acetate (PMA) accompanied by changes different from typical apoptosis or necrosis. *J Leukoc Biol* 1996; **59**: 229-240 [PMID: 8603995 DOI: 10.1002/jlb.59.2.229]

35 **Sollberger G**, Tilley DO, Zychlinsky A. Neutrophil Extracellular Traps: The Biology of Chromatin Externalization. *Dev Cell* 2018; **44**: 542-553 [PMID: 29533770 DOI: 10.1016/j.devcel.2018.01.019]

36 **Yipp BG**, Kubes P. NETosis: how vital is it? *Blood* 2013; **122**: 2784-2794 [PMID: 24009232 DOI: 10.1182/blood-2013-04-457671]

37 **Pilsczek FH**, Salina D, Poon KK, Fahey C, Yipp BG, Sibley CD, Robbins SM, Green FH, Surette MG, Sugai M, Bowden MG, Hussain M, Zhang K, Kubes P. A novel mechanism of rapid nuclear neutrophil extracellular trap formation in response to Staphylococcus aureus. *J Immunol* 2010; **185**: 7413-7425 [PMID: 21098229 DOI: 10.4049/jimmunol.1000675]

38 **Neubert E**, Meyer D, Rocca F, Günay G, Kwaczala-Tessmann A, Grandke J, Senger-Sander S, Geisler C, Egner A, Schön MP, Erpenbeck L, Kruss S. Chromatin swelling drives neutrophil extracellular trap release. *Nat Commun* 2018; **9**: 3767 [PMID: 30218080 DOI: 10.1038/s41467-018-06263-5]

39 **Granger V**, Faille D, Marani V, Noël B, Gallais Y, Szely N, Flament H, Pallardy M, Chollet-Martin S, de Chaisemartin L. Human blood monocytes are able to form extracellular traps. *J Leukoc Biol* 2017; **102**: 775-781 [PMID: 28465447 DOI: 10.1189/jlb.3MA0916-411R]

40 **von Köckritz-Blickwede M**, Goldmann O, Thulin P, Heinemann K, Norrby-Teglund A, Rohde M, Medina E. Phagocytosis-independent antimicrobial activity of mast cells by means of extracellular trap formation. *Blood* 2008; **111**: 3070-3080 [PMID: 18182576 DOI: 10.1182/blood-2007-07-104018]

41 **Yousefi S**, Gold JA, Andina N, Lee JJ, Kelly AM, Kozlowski E, Schmid I, Straumann A, Reichenbach J, Gleich GJ, Simon HU. Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. *Nat Med* 2008; **14**: 949-953 [PMID: 18690244 DOI: 10.1038/nm.1855]

42 **Halverson TW**, Wilton M, Poon KK, Petri B, Lewenza S. DNA is an antimicrobial component of neutrophil extracellular traps. *PLoS Pathog* 2015; **11**: e1004593 [PMID: 25590621 DOI: 10.1371/journal.ppat.1004593]

43 **McDonald B**, Urrutia R, Yipp BG, Jenne CN, Kubes P. Intravascular neutrophil extracellular traps capture bacteria from the bloodstream during sepsis. *Cell Host Microbe* 2012; **12**: 324-333 [PMID: 22980329 DOI: 10.1016/j.chom.2012.06.011]

44 **Papayannopoulos V**, Metzler KD, Hakkim A, Zychlinsky A. Neutrophil elastase and myeloperoxidase regulate the formation of neutrophil extracellular traps. *J Cell Biol* 2010; **191**: 677-691 [PMID: 20974816 DOI: 10.1083/jcb.201006052]

45 **Hakkim A**, Fürnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V, Herrmann M, Voll RE, Zychlinsky A. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. *Proc Natl Acad Sci USA* 2010; **107**: 9813-9818 [PMID: 20439745 DOI: 10.1073/pnas.0909927107]

46 **Demers M**, Krause DS, Schatzberg D, Martinod K, Voorhees JR, Fuchs TA, Scadden DT, Wagner DD. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. *Proc Natl Acad Sci USA* 2012; **109**: 13076-13081 [PMID: 22826226 DOI: 10.1073/pnas.1200419109]

47 **Leal AC**, Mizurini DM, Gomes T, Rochael NC, Saraiva EM, Dias MS, Werneck CC, Sielski MS, Vicente CP, Monteiro RQ. Tumour-Derived Exosomes Induce the Formation of Neutrophil Extracellular Traps: Implications For The Establishment of Cancer-Associated Thrombosis. *Sci Rep* 2017; **7**: 6438 [PMID: 28743887 DOI: 10.1038/s41598-017-06893-7]

48 **Sanmamed MF**, Carranza-Rua O, Alfaro C, Oñate C, Martín-Algarra S, Perez G, Landazuri SF, Gonzalez A, Gross S, Rodriguez I, Muñoz-Calleja C, Rodríguez-Ruiz M, Sangro B, López-Picazo JM, Rizzo M, Mazzolini G, Pascual JI, Andueza MP, Perez-Gracia JL, Melero I. Serum interleukin-8 reflects tumour burden and treatment response across malignancies of multiple tissue origins. *Clin Cancer Res* 2014; **20**: 5697-5707 [PMID: 25224278 DOI: 10.1158/1078-0432.CCR-13-3203]

49 **Alfaro C**, Teijeira A, Oñate C, Pérez G, Sanmamed MF, Andueza MP, Alignani D, Labiano S, Azpilikueta A, Rodriguez-Paulete A, Garasa S, Fusco JP, Aznar A, Inogés S, De Pizzol M, Allegretti M, Medina-Echeverz J, Berraondo P, Perez-Gracia JL, Melero I. Tumour-Produced Interleukin-8 Attracts Human Myeloid-Derived Suppressor Cells and Elicits Extrusion of Neutrophil Extracellular Traps (NETs). *Clin Cancer Res* 2016; **22**: 3924-3936 [PMID: 26957562 DOI: 10.1158/1078-0432.CCR-15-2463]

50 **Cai Z**, Zhang M, Boafo Kwantwi L, Bi X, Zhang C, Cheng Z, Ding X, Su T, Wang H, Wu Q. Breast cancer cells promote self-migration by secreting interleukin 8 to induce NET formation. *Gene* 2020; **754**: 144902 [PMID: 32544496 DOI: 10.1016/j.gene.2020.144902]

51 **Zha C**, Meng X, Li L, Mi S, Qian D, Li Z, Wu P, Hu S, Zhao S, Cai J, Liu Y. Neutrophil extracellular traps mediate the crosstalk between glioma progression and the tumour microenvironment **via** the HMGB1/RAGE/IL-8 axis. *Cancer Biol Med* 2020; **17**: 154-168 [PMID: 32296583 DOI: 10.20892/j.issn.2095-3941.2019.0353]

52 **Zhang Q**, Liu S, Parajuli KR, Zhang W, Zhang K, Mo Z, Liu J, Chen Z, Yang S, Wang AR, Myers L, You Z. Interleukin-17 promotes prostate cancer *via* MMP7-induced epithelial-to-mesenchymal transition. *Oncogene* 2017; **36**: 687-699 [PMID: 27375020 DOI: 10.1038/onc.2016.240]

53 **Zhang Y**, Chandra V, Riquelme Sanchez E, Dutta P, Quesada PR, Rakoski A, Zoltan M, Arora N, Baydogan S, Horne W, Burks J, Xu H, Hussain P, Wang H, Gupta S, Maitra A, Bailey JM, Moghaddam SJ, Banerjee S, Sahin I, Bhattacharya P, McAllister F. Interleukin-17-induced neutrophil extracellular traps mediate resistance to checkpoint blockade in pancreatic cancer. *J Exp Med* 2020; **217**: e20190354 [PMID: 32860704 DOI: 10.1084/jem.20190354]

54 **Rocks N**, Vanwinge C, Radermecker C, Blacher S, Gilles C, Marée R, Gillard A, Evrard B, Pequeux C, Marichal T, Noel A, Cataldo D. Ozone-primed neutrophils promote early steps of tumour cell metastasis to lungs by enhancing their NET production. *Thorax* 2019; **74**: 768-779 [PMID: 31142617 DOI: 10.1136/thoraxjnl-2018-211990]

55 **Hudock KM**, Collins MS, Imbrogno M, Snowball J, Kramer EL, Brewington JJ, Gollomp K, McCarthy C, Ostmann AJ, Kopras EJ, Davidson CR, Srdiharan A, Arumugam P, Sengupta S, Xu Y, Worthen GS, Trapnell BC, Clancy JP. Neutrophil extracellular traps activate IL-8 and IL-1 expression in human bronchial epithelia. *Am J Physiol Lung Cell Mol Physiol* 2020; **319**: L137-L147 [PMID: 32159969 DOI: 10.1152/ajplung.00144.2019]

56 **Hosseinzadeh A**, Thompson PR, Segal BH, Urban CF. Nicotine induces neutrophil extracellular traps. *J Leukoc Biol* 2016; **100**: 1105-1112 [PMID: 27312847 DOI: 10.1189/jlb.3AB0815-379RR]

57 **Yotsumoto S**, Muroi Y, Chiba T, Ohmura R, Yoneyama M, Magarisawa M, Dodo K, Terayama N, Sodeoka M, Aoyagi R, Arita M, Arakawa S, Shimizu S, Tanaka M. Hyperoxidation of ether-linked phospholipids accelerates neutrophil extracellular trap formation. *Sci Rep* 2017; **7**: 16026 [PMID: 29167447 DOI: 10.1038/s41598-017-15668-z]

58 **Yasuda H**, Takishita Y, Morita A, Tsutsumi T, Tsuchiya M, Sato EF. DNA demethylation increases NETosis. *Arch Biochem Biophys* 2020; **689**: 108465 [PMID: 32561201 DOI: 10.1016/j.abb.2020.108465]

59 **Smyth EC**, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 2020; **396**: 635-648 [PMID: 32861308 DOI: 10.1016/S0140-6736(20)31288-5]

60 **Agnelli G**, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, Cohen A, Bauersachs R, Brenner B, Torbicki A, Sueiro MR, Lambert C, Gussoni G, Campanini M, Fontanella A, Vescovo G, Verso M; Caravaggio Investigators. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N Engl J Med* 2020; **382**: 1599-1607 [PMID: 32223112 DOI: 10.1056/NEJMoa1915103]

61 **Kwon HC**, Oh SY, Lee S, Kim SH, Han JY, Koh RY, Kim MC, Kim HJ. Plasma levels of prothrombin fragment F1+2, D-dimer and prothrombin time correlate with clinical stage and lymph node metastasis in operable gastric cancer patients. *Jpn J Clin Oncol* 2008; **38**: 2-7 [PMID: 18258711 DOI: 10.1093/jjco/hym157]

62 **Lee KW**, Bang SM, Kim S, Lee HJ, Shin DY, Koh Y, Lee YG, Cha Y, Kim YJ, Kim JH, Park DJ, Kim HH, Oh D, Lee JS. The incidence, risk factors and prognostic implications of venous thromboembolism in patients with gastric cancer. *J Thromb Haemost* 2010; **8**: 540-547 [PMID: 20040044 DOI: 10.1111/j.1538-7836.2009.03731.x]

63 **Ay C**, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. *Thromb Haemost* 2017; **117**: 219-230 [PMID: 27882374 DOI: 10.1160/TH16-08-0615]

64 **Yang C**, Sun W, Cui W, Li X, Yao J, Jia X, Li C, Wu H, Hu Z, Zou X. Procoagulant role of neutrophil extracellular traps in patients with gastric cancer. *Int J Clin Exp Pathol* 2015; **8**: 14075-14086 [PMID: 26823721]

65 **Kanda M**, Shimizu D, Tanaka H, Tanaka C, Kobayashi D, Hayashi M, Iwata N, Niwa Y, Yamada S, Fujii T, Sugimoto H, Murotani K, Fujiwara M, Kodera Y. Significance of SYT8 For the Detection, Prediction, and Treatment of Peritoneal Metastasis From Gastric Cancer. *Ann Surg* 2018; **267**: 495-503 [PMID: 28026832 DOI: 10.1097/SLA.0000000000002096]

66 **Gamboa AC**, Winer JH. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer. *Cancers (Basel)* 2019; **11**: 1662 [PMID: 31717799 DOI: 10.3390/cancers11111662]

67 **Ilson DH**. Advances in the treatment of gastric cancer: 2019. *Curr Opin Gastroenterol* 2019; **35**: 551-554 [PMID: 31436556 DOI: 10.1097/MOG.0000000000000577]

68 **Kanamaru R**, Ohzawa H, Miyato H, Matsumoto S, Haruta H, Kurashina K, Saito S, Hosoya Y, Yamaguchi H, Yamashita H, Seto Y, Lefor AK, Sata N, Kitayama J. Low density neutrophils (LDN) in postoperative abdominal cavity assist the peritoneal recurrence through the production of neutrophil extracellular traps (NETs). *Sci Rep* 2018; **8**: 632 [PMID: 29330531 DOI: 10.1038/s41598-017-19091-2]

69 **Kanamaru R**, Ohzawa H, Miyato H, Yamaguchi H, Hosoya Y, Lefor AK, Sata N, Kitayama J. Neutrophil Extracellular Traps Generated by Low Density Neutrophils Obtained from Peritoneal Lavage Fluid Mediate Tumour Cell Growth and Attachment. *J Vis Exp* 2018; **(138)**: 58201 [PMID: 30124642 DOI: 10.3791/58201]

70 **Goldfarb Y**, Sorski L, Benish M, Levi B, Melamed R, Ben-Eliyahu S. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. *Ann Surg* 2011; **253**: 798-810 [PMID: 21475023 DOI: 10.1097/SLA.0b013e318211d7b5]

71 **Angele MK**, Faist E. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. *Crit Care* 2002; **6**: 298-305 [PMID: 12225603 DOI: 10.1186/cc1514]

72 **Kumagai Y**, Ohzawa H, Miyato H, Horie H, Hosoya Y, Lefor AK, Sata N, Kitayama J. Surgical Stress Increases Circulating Low-Density Neutrophils Which May Promote Tumour Recurrence. *J Surg Res* 2020; **246**: 52-61 [PMID: 31561178 DOI: 10.1016/j.jss.2019.08.022]

73 **Chen X**, Guo J, Bao J, Lu J, Wang Y. The anticancer properties of Salvia miltiorrhiza Bunge (Danshen): a systematic review. *Med Res Rev* 2014; **34**: 768-794 [PMID: 24123144 DOI: 10.1002/med.21304]

74 **Tao L**, Xu M, Dai X, Ni T, Li D, Jin F, Wang H, Tao L, Pan B, Woodgett JR, Qian Y, Liu Y. Polypharmacological Profiles Underlying the Antitumour Property of *Salvia miltiorrhiza* Root (Danshen) Interfering with NOX-Dependent Neutrophil Extracellular Traps. *Oxid Med Cell Longev* 2018; **2018**: 4908328 [PMID: 30210653 DOI: 10.1155/2018/4908328]

75 **Du XY**, Liu X, Wang ZJ, Wang YY. SLPI promotes the gastric cancer growth and metastasis by regulating the expression of P53, Bcl-2 and Caspase-8. *Eur Rev Med Pharmacol Sci* 2017; **21**: 1495-1501 [PMID: 28429358]

76 **Lu C**, Cai D, Ma J. Pachymic Acid Sensitizes Gastric Cancer Cells to Radiation Therapy by Upregulating Bax through Hypoxia. *Am J Chin Med* 2018; **46**: 875-890 [PMID: 29737213 DOI: 10.1142/S0192415X18500465]

77 **Sokolova O**, Naumann M. NF-κB Signaling in Gastric Cancer. *Toxins (Basel)* 2017; **9**: 119 [PMID: 28350359 DOI: 10.3390/toxins9040119]

78 **Li R**, Zou X, Zhu T, Xu H, Li X, Zhu L. Destruction of Neutrophil Extracellular Traps Promotes the Apoptosis and Inhibits the Invasion of Gastric Cancer Cells by Regulating the Expression of Bcl-2, Bax and NF-κB. *Onco Targets Ther* 2020; **13**: 5271-5281 [PMID: 32606746 DOI: 10.2147/OTT.S227331]

79 **Ünlü B**, van Es N, Arindrarto W, Kiełbasa SM, Mei H, Westerga J, Middeldorp S, Kuppen PJK, Otten JMMB, Cannegieter S, Versteeg HH. Genes associated with venous thromboembolism in colorectal cancer patients. *J Thromb Haemost* 2018; **16**: 293-302 [PMID: 29247594 DOI: 10.1111/jth.13926]

80 **Zhang Y**, Wang C, Yu M, Zhao X, Du J, Li Y, Jing H, Dong Z, Kou J, Bi Y, Novakovic VA, Zhou J, Shi J. Neutrophil extracellular traps induced by activated platelets contribute to procoagulant activity in patients with colorectal cancer. *Thromb Res* 2019; **180**: 87-97 [PMID: 31271975 DOI: 10.1016/j.thromres.2019.06.005]

81 **Arelaki S**, Arampatzioglou A, Kambas K, Papagoras C, Miltiades P, Angelidou I, Mitsios A, Kotsianidis I, Skendros P, Sivridis E, Maroulakou I, Giatromanolaki A, Ritis K. Gradient Infiltration of Neutrophil Extracellular Traps in Colon Cancer and Evidence for Their Involvement in Tumour Growth. *PLoS One* 2016; **11**: e0154484 [PMID: 27136460 DOI: 10.1371/journal.pone.0154484]

82 **Rayes RF**, Mouhanna JG, Nicolau I, Bourdeau F, Giannias B, Rousseau S, Quail D, Walsh L, Sangwan V, Bertos N, Cools-Lartigue J, Ferri LE, Spicer JD. Primary tumours induce neutrophil extracellular traps with targetable metastasis promoting effects. *JCI Insight* 2019; **5**: e128008 [PMID: 31343990 DOI: 10.1172/jci.insight.128008]

83 **Tohme S**, Yazdani HO, Al-Khafaji AB, Chidi AP, Loughran P, Mowen K, Wang Y, Simmons RL, Huang H, Tsung A. Neutrophil Extracellular Traps Promote the Development and Progression of Liver Metastases after Surgical Stress. *Cancer Res* 2016; **76**: 1367-1380 [PMID: 26759232 DOI: 10.1158/0008-5472.CAN-15-1591]

84 **Richardson JJR**, Hendrickse C, Gao-Smith F, Thickett DR. Characterization of systemic neutrophil function in patients undergoing colorectal cancer resection. *J Surg Res* 2017; **220**: 410-418 [PMID: 28890131 DOI: 10.1016/j.jss.2017.07.036]

85 **Cheng KJ**, Alshawsh MA, Mejia Mohamed EH, Thavagnanam S, Sinniah A, Ibrahim ZA. HMGB1: an overview of its versatile roles in the pathogenesis of colorectal cancer. *Cell Oncol (Dordr)* 2020; **43**: 177-193 [PMID: 31677065 DOI: 10.1007/s13402-019-00477-5]

86 **Ni Q**, Zhang F, Liu Y, Wang Z, Yu G, Liang B, Niu G, Su T, Zhu G, Lu G, Zhang L, Chen X. A bi-adjuvant nanovaccine that potentiates immunogenicity of neoantigen for combination immunotherapy of colorectal cancer. *Sci Adv* 2020; **6**: eaaw6071 [PMID: 32206706 DOI: 10.1126/sciadv.aaw6071]

87 **Chrysanthopoulou A**, Kambas K, Stakos D, Mitroulis I, Mitsios A, Vidali V, Angelidou I, Bochenek M, Arelaki S, Arampatzioglou A, Galani IE, Skendros P, Couladouros EA, Konstantinides S, Andreakos E, Schäfer K, Ritis K. Interferon lambda1/IL-29 and inorganic polyphosphate are novel regulators of neutrophil-driven thromboinflammation. *J Pathol* 2017; **243**: 111-122 [PMID: 28678391 DOI: 10.1002/path.4935]

88 **Arelaki S**, Arampatzioglou A, Kambas K, Sivridis E, Giatromanolaki A, Ritis K. Mast cells co-expressing CD68 and inorganic polyphosphate are linked with colorectal cancer. *PLoS One* 2018; **13**: e0193089 [PMID: 29543850 DOI: 10.1371/journal.pone.0193089]

89 **Yazdani HO**, Roy E, Comerci AJ, van der Windt DJ, Zhang H, Huang H, Loughran P, Shiva S, Geller DA, Bartlett DL, Tsung A, Sheng T, Simmons RL, Tohme S. Neutrophil Extracellular Traps Drive Mitochondrial Homeostasis in Tumours to Augment Growth. *Cancer Res* 2019; **79**: 5626-5639 [PMID: 31519688 DOI: 10.1158/0008-5472.CAN-19-0800]

90 **Li J**, Huang L, Zhao H, Yan Y, Lu J. The Role of Interleukins in Colorectal Cancer. *Int J Biol Sci* 2020; **16**: 2323-2339 [PMID: 32760201 DOI: 10.7150/ijbs.46651]

91 **Yang L**, Liu L, Zhang R, Hong J, Wang Y, Wang J, Zuo J, Zhang J, Chen J, Hao H. IL-8 mediates a positive loop connecting increased neutrophil extracellular traps (NETs) and colorectal cancer liver metastasis. *J Cancer* 2020; **11**: 4384-4396 [PMID: 32489457 DOI: 10.7150/jca.44215]

92 **Shang A**, Gu C, Zhou C, Yang Y, Chen C, Zeng B, Wu J, Lu W, Wang W, Sun Z, Li D. Exosomal KRAS mutation promotes the formation of tumour-associated neutrophil extracellular traps and causes deterioration of colorectal cancer by inducing IL-8 expression. *Cell Commun Signal* 2020; **18**: 52 [PMID: 32228650 DOI: 10.1186/s12964-020-0517-1]

93 **Yang L**, Liu Q, Zhang X, Liu X, Zhou B, Chen J, Huang D, Li J, Li H, Chen F, Liu J, Xing Y, Chen X, Su S, Song E. DNA of neutrophil extracellular traps promotes cancer metastasis *via* CCDC25. *Nature* 2020; **583**: 133-138 [PMID: 32528174 DOI: 10.1038/s41586-020-2394-6]

94 **Zhang Y**, Hu Y, Ma C, Sun H, Wei X, Li M, Wei W, Zhang F, Yang F, Wang H, Gu K. Diagnostic, Therapeutic Predictive, and Prognostic Value of Neutrophil Extracellular Traps in Patients With Gastric Adenocarcinoma. *Front Oncol* 2020; **10**: 1036 [PMID: 32714865 DOI: 10.3389/fonc.2020.01036]

95 **Decker AS**, Pylaeva E, Brenzel A, Spyra I, Droege F, Hussain T, Lang S, Jablonska J. Prognostic Role of Blood NETosis in the Progression of Head and Neck Cancer. *Cells* 2019; **8**: 946 [PMID: 31438586 DOI: 10.3390/cells8090946]

96 **Jin W**, Xu HX, Zhang SR, Li H, Wang WQ, Gao HL, Wu CT, Xu JZ, Qi ZH, Li S, Ni QX, Liu L, Yu XJ. Tumour-Infiltrating NETs Predict Postsurgical Survival in Patients with Pancreatic Ductal Adenocarcinoma. *Ann Surg Oncol* 2019; **26**: 635-643 [PMID: 30374923 DOI: 10.1245/s10434-018-6941-4]

97 **Zhang H**, Lv H, Weng M, Wang H, Cata JP, Chen W, Miao C. Preoperative leukocytosis is associated with increased tumour-infiltrating neutrophil extracellular traps and worse outcomes in esophageal cancer. *Ann Transl Med* 2020; **8**: 441 [PMID: 32395485 DOI: 10.21037/atm.2020.03.190]

98 **Abu Abed U**, Brinkmann V. Immunofluorescence Labelling of Human and Murine Neutrophil Extracellular Traps in Paraffin-Embedded Tissue. *J Vis Exp* 2019 [PMID: 31566594 DOI: 10.3791/60115]

99 **Elsherif L**, Sciaky N, Metts CA, Modasshir M, Rekleitis I, Burris CA, Walker JA, Ramadan N, Leisner TM, Holly SP, Cowles MW, Ataga KI, Cooper JN, Parise LV. Machine Learning to Quantitate Neutrophil NETosis. *Sci Rep* 2019; **9**: 16891 [PMID: 31729453 DOI: 10.1038/s41598-019-53202-5]

100 **Thålin C**, Lundström S, Seignez C, Daleskog M, Lundström A, Henriksson P, Helleday T, Phillipson M, Wallén H, Demers M. Citrullinated histone H3 as a novel prognostic blood marker in patients with advanced cancer. *PLoS One* 2018; **13**: e0191231 [PMID: 29324871 DOI: 10.1371/journal.pone.0191231]

101 **Grilz E**, Mauracher LM, Posch F, Königsbrügge O, Zöchbauer-Müller S, Marosi C, Lang I, Pabinger I, Ay C. Citrullinated histone H3, a biomarker for neutrophil extracellular trap formation, predicts the risk of mortality in patients with cancer. *Br J Haematol* 2019; **186**: 311-320 [PMID: 30968400 DOI: 10.1111/bjh.15906]

102 **Mauracher LM**, Posch F, Martinod K, Grilz E, Däullary T, Hell L, Brostjan C, Zielinski C, Ay C, Wagner DD, Pabinger I, Thaler J. Citrullinated histone H3, a biomarker of neutrophil extracellular trap formation, predicts the risk of venous thromboembolism in cancer patients. *J Thromb Haemost* 2018; **16**: 508-518 [PMID: 29325226 DOI: 10.1111/jth.13951]

103 **Li M**, Lin C, Leso A, Nefedova Y. Quantification of Citrullinated Histone H3 Bound DNA for Detection of Neutrophil Extracellular Traps. *Cancers (Basel)* 2020; **12**: 3424 [PMID: 33218159 DOI: 10.3390/cancers12113424]

104 **Davis JC Jr**, Manzi S, Yarboro C, Rairie J, Mcinnes I, Averthelyi D, Sinicropi D, Hale VG, Balow J, Austin H, Boumpas DT, Klippel JH. Recombinant human Dnase I (rhDNase) in patients with lupus nephritis. *Lupus* 1999; **8**: 68-76 [PMID: 10025601 DOI: 10.1191/096120399678847380]

105 **Xia Y**, He J, Zhang H, Wang H, Tetz G, Maguire CA, Wang Y, Onuma A, Genkin D, Tetz V, Stepanov A, Terekhov S, Ukrainskaya V, Huang H, Tsung A. AAV-mediated gene transfer of DNase I in the liver of mice with colorectal cancer reduces liver metastasis and restores local innate and adaptive immune response. *Mol Oncol* 2020; **14**: 2920-2935 [PMID: 32813937 DOI: 10.1002/1878-0261.12787]

106 **Schauer C**, Janko C, Munoz LE, Zhao Y, Kienhöfer D, Frey B, Lell M, Manger B, Rech J, Naschberger E, Holmdahl R, Krenn V, Harrer T, Jeremic I, Bilyy R, Schett G, Hoffmann M, Herrmann M. Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. *Nat Med* 2014; **20**: 511-517 [PMID: 24784231 DOI: 10.1038/nm.3547]

107 **Okeke EB**, Louttit C, Fry C, Najafabadi AH, Han K, Nemzek J, Moon JJ. Inhibition of neutrophil elastase prevents neutrophil extracellular trap formation and rescues mice from endotoxic shock. *Biomaterials* 2020; **238**: 119836 [PMID: 32045782 DOI: 10.1016/j.biomaterials.2020.119836]

108 **Fuchs TA**, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, Weinrauch Y, Brinkmann V, Zychlinsky A. Novel cell death program leads to neutrophil extracellular traps. *J Cell Biol* 2007; **176**: 231-241 [PMID: 17210947 DOI: 10.1083/jcb.200606027]

109 **Metzler KD**, Fuchs TA, Nauseef WM, Reumaux D, Roesler J, Schulze I, Wahn V, Papayannopoulos V, Zychlinsky A. Myeloperoxidase is required for neutrophil extracellular trap formation: implications for innate immunity. *Blood* 2011; **117**: 953-959 [PMID: 20974672 DOI: 10.1182/blood-2010-06-290171]

110 **Hakkim A**, Fuchs TA, Martinez NE, Hess S, Prinz H, Zychlinsky A, Waldmann H. Activation of the Raf-MEK-ERK pathway is required for neutrophil extracellular trap formation. *Nat Chem Biol* 2011; **7**: 75-77 [PMID: 21170021 DOI: 10.1038/nchembio.496]

111 **Martinez NE**, Zimmermann TJ, Goosmann C, Alexander T, Hedberg C, Ziegler S, Zychlinsky A, Waldmann H. Tetrahydroisoquinolines: New Inhibitors of Neutrophil Extracellular Trap (NET) Formation. *Chembiochem* 2017; **18**: 888-893 [PMID: 28240414 DOI: 10.1002/cbic.201600650]

112 **Khan MA**, D'Ovidio A, Tran H, Palaniyar N. Anthracyclines Suppress Both NADPH Oxidase-Dependent and -Independent NETosis in Human Neutrophils. *Cancers (Basel)* 2019; **11**: 1328 [PMID: 31500300 DOI: 10.3390/cancers11091328]

113 **Rayes RF**, Vourtzoumis P, Bou Rjeily M, Seth R, Bourdeau F, Giannias B, Berube J, Huang YH, Rousseau S, Camilleri-Broet S, Blumberg RS, Beauchemin N, Najmeh S, Cools-Lartigue J, Spicer JD, Ferri LE. Neutrophil Extracellular Trap-Associated CEACAM1 as a Putative Therapeutic Target to Prevent Metastatic Progression of Colon Carcinoma. *J Immunol* 2020; **204**: 2285-2294 [PMID: 32169849 DOI: 10.4049/jimmunol.1900240]

114 **Li Y**, Li M, Weigel B, Mall M, Werth VP, Liu ML. Nuclear envelope rupture and NET formation is driven by PKCα-mediated lamin B disassembly. *EMBO Rep* 2020; **21**: e48779 [PMID: 32537912 DOI: 10.15252/embr.201948779]

115 **Basyreva LY**, Voinova EV, Gusev AA, Mikhalchik EV, Kuskov AN, Goryachaya AV, Gusev SA, Shtilman MI, Velonia K, Tsatsakis AM. Fluorouracil neutrophil extracellular traps formation inhibited by polymer nanoparticle shielding. *Mater Sci Eng C Mater Biol Appl* 2020; **108**: 110382 [PMID: 31924010 DOI: 10.1016/j.msec.2019.110382]

116 **Cao TM**, King MR. Supercharged eGFP-TRAIL Decorated NETs to Ensnare and Kill Disseminated Tumour Cells. *Cell Mol Bioeng* 2020; **13**: 359-367 [PMID: 32952735 DOI: 10.1007/s12195-020-00639-8]

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