Inflammation et cancer

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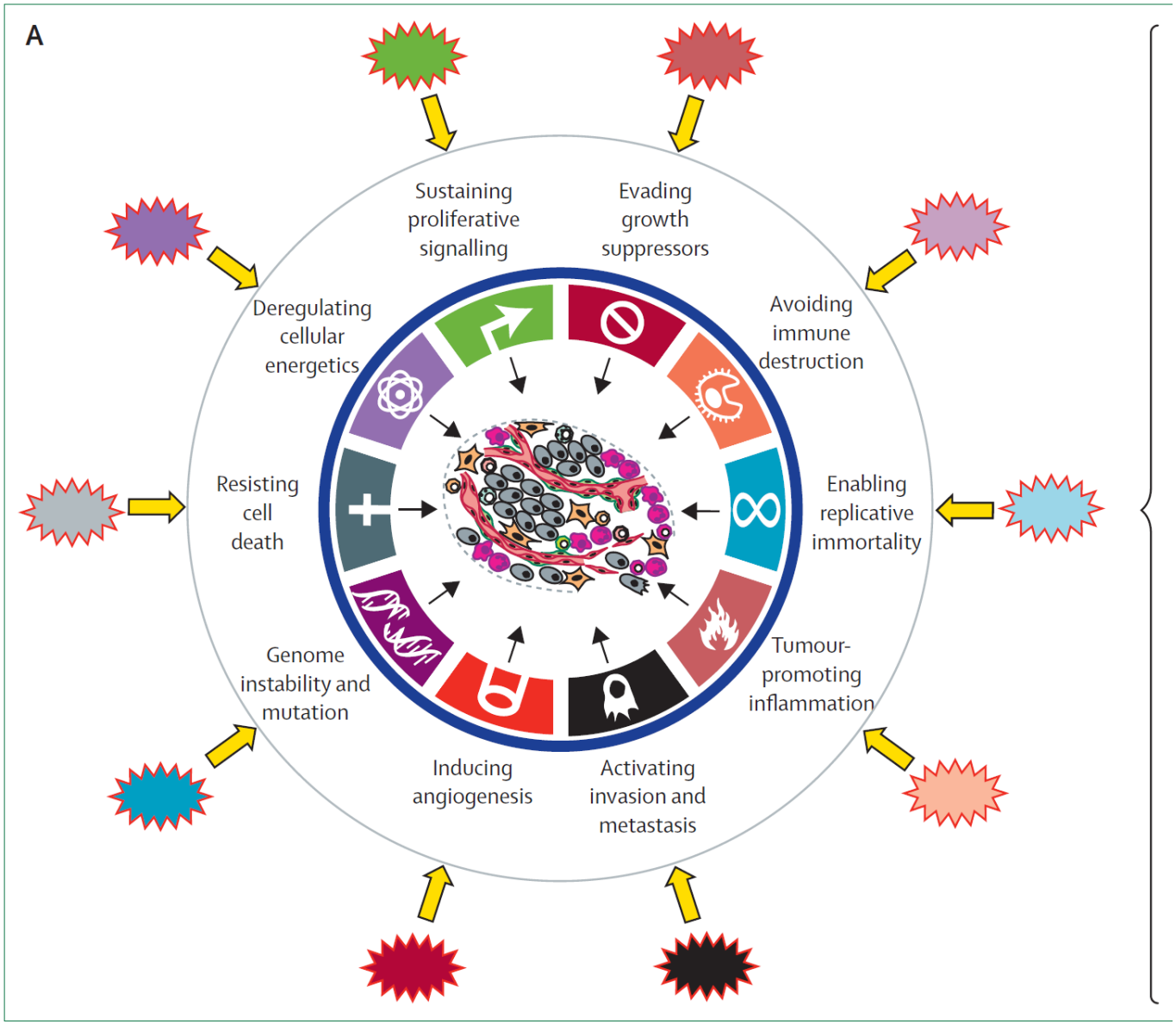

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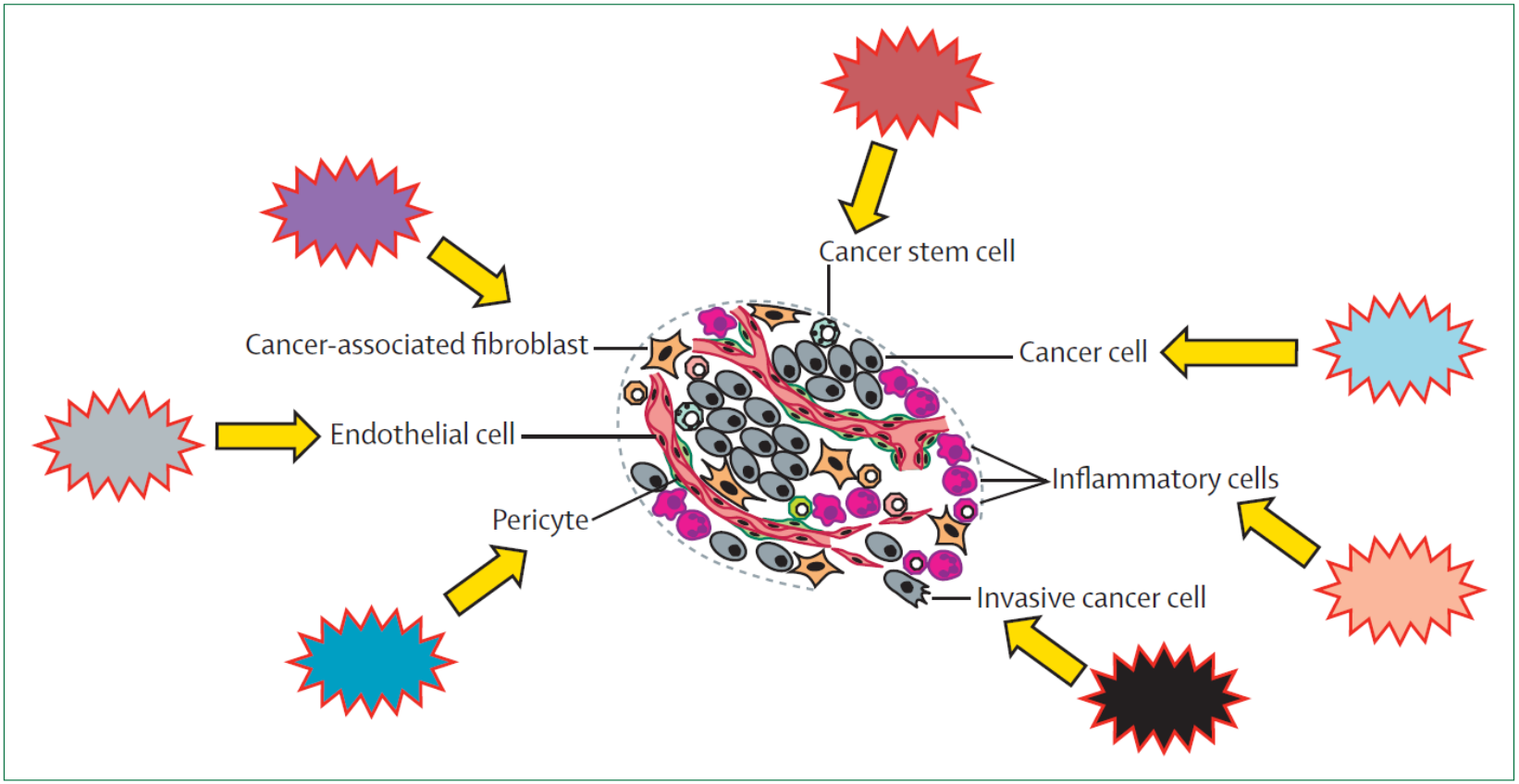

Figure 2: Targeting of cancer's armed forces

De mauvais pronostic

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Laboratory-Clinic Interface

The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer

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Table 1
Systemic inflammation based prognostic scores, the Glasgow Prognostic Scores.

The Glasgow Prognostic Score (GPS)	Points allocated
C-Reactive protein $\geqslant$10 mg/l and albumin $\geqslant$35 g/l	0
C-Reactive protein >10 mg/l	1
Albumin <35 g/l	1
C-Reactive protein >10 mg/l and albumin <35 g/l	2
The modified Glasgow Prognostic Score (mGPS)	
C-Reactive protein $\leqslant$ 10 mg/l and albumin $\geqslant$35 g/l	0
C-Reactive protein >10 mg/l	1
C-Reactive protein >10 mg/l and albumin <35 g/l	2

Table 2
Studies ($n = 4$) of the prognostic value of the GPS/mGPS, in unselected cohorts of patients with cancer ($n > 19{,}400$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
Crumley et al.[15]	Glasgow, UK	Gastro-oesophageal	217	1.7 (<0.001)	mGPS predicted survival independent of tumour site/stage/treatment
Proctor et al.[16]	Glasgow, UK	11 sites	9608	1.9 (<0.001)	mGPS predicted survival independent of tumour site
Proctor et al.[17]	Glasgow, UK	11 sites	8759	1.7 (<0.001)	mGPS predicted survival superior to NLR, PLR, PI, PNI
Shafique et al.[18]	Glasgow, UK	Prostate	897	1.8 (<0.05)	mGPS predicted survival superior to NLR

HR multivariate hazard ratio for incremental change of GPS/mGPS.

Table 3
Studies ($n = 28$) of the prognostic value of the GPS/mGPS in patients with operable cancer ($n > 8{,}000$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
McMillan et al.[14]	Glasgow, UK	Colorectal	316	1.7 (<0.001)	mGPS predicted survival independent of stage/treatment
Leitch et al.[19]	Glasgow, UK	Colorectal	233	2.1 (<0.001)	mGPS predicted survival superior to WCC/lymphocytes
Ishizuka et al.[20]	Tochigi, Japan	Colorectal	315	1.5 (<0.01)	GPS predicted survival independent of stage/treatment
Crozier et al.[21]	Glasgow, UK	Colorectal	188	2.2 (<0.05)	mGPS predicted survival independent of emergency presentation
Roxburgh et al.[22]	Glasgow, UK	Colorectal	244	2.3 (<0.001)	mGPS predicted survival independent of Petersen Index
Moyes et al.[23]	Glasgow, UK	Colorectal	455	1.8 (<0.01)	mGPS predicted post-operative infective complications
Roxburgh et al.[24]	Glasgow, UK	Colorectal	287	2.7 (<0.001)	mGPS predicted survival independent of tumour inflammatory infiltrate
Ishizuka et al.[25]	Tochigi, Japan	Colorectal liver	300	2.1 (<0.05)	GPS predicted survival independent of CLIP score
Ishizuka et al.[26]	Tochigi, Japan	Colorectal	156	24.5 (<0.05)	GPS predicted survival in T1/T2 stage disease
Kobayashi et al.[27]	Tokyo, Japan	Oesophageal	65	NR (<0.001)	GPS predicted survival independent of lymph node status
Polterauer et al.[28]	Vienna, Austria	Cervical	244	NR (<0.05)	GPS predicted survival independent of FIGO stage
Kobayashi et al.[29]	Tokyo, Japan	Colorectal liver	63	3.1 (<0.01)	GPS predicted survival independent of number of liver metastases
Knight et al.[30]	Manchester, UK	Pancreas	99	4.3 (<0.05)	GPS predicted post-operative morbidity
Richards et al.[31]	Glasgow, UK	Colorectal	320	1.8 (<0.001)	mGPS predicted survival independent of POSSUM
Nozoe et al.[32]	Koga, Japan	Gastric	232	4.1 (<0.001)	mGPS predicted survival independent of tumour stage
Moug et al.[33]	Kilmarnock, UK	Colorectal	206	1.6 (<0.05)	mGPS predicted survival independent of LNR
Roxburgh et al.[34]	Glasgow, UK	Colorectal	302	1.6 (<0.001)	mGPS predicted survival independent of comorbidity indices
Vashist et al.[35]	Hamburg, Germany	Oesophageal	495	3.0 (<0.001)	GPS predicted peri-operative morbidity and survival
Ishizuka et al.[36]	Tochigi, Japan	Hepatocellular	300	2.1 (<0.05)	GPS predicted survival independent of post-operative mortality
Dutta et al.[37]	Glasgow, UK	Oesophageal	112	4.3 (<0.001)	mGPS predicted survival independent of LNR, NLR and PLR
Jamieson et al.[38]	Glasgow, UK	Pancreas	135	2.3 (<0.001)	GPS predicted survival independent of margin status/adjuvant therapy
Ishizuka et al.[39]	Tochigi, Japan	Hepatocellular	398	2.5 (<0.05)	GPS predicted survival independent of CLIP score
Lamb et al.[40]	Glasgow, UK	Renal	169	5.1 (<0.001)	GPS predicted survival independent of established scoring systems
La Torre et al.[41]	Rome, Italy	Pancreas	101	1.8 (<0.01)	mGPS predicted survival independent of LNR and margin status
Wang et al.[42]	Guangzhou, China	Gastric	324	1.4 (<0.01)	GPS predicted survival independent of TNM stage, NLR and PLR
Jamieson et al.[43]	Glasgow, UK	Pancreas	173	1.8 (<0.01)	mGPS predicted survival independent of LIR
Ishizuka et al.[44]	Tochigi, Japan	Colorectal	271	2.0 (<0.05)	mGPS predicted survival in patients with normal CEA
Dutta et al.[45]	Glasgow, UK	Gastric	120	2.2 (<0.01)	mGPS predicted survival independent of LNR, NLR and PLR
Jiang et al.[46]	Tokyo, Japan	Gastric	1710	1.8 (<0.01)	mGPS predicted survival independent of TNM stage

HR, multivariate hazard ratio for incremental change of GPS/mGPS; NR, not reported; LNR, lymph node ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; CLIP, cancer of the liver Italian program; LIR, local inflammatory response; POSSUM.

Table 4
Studies ($n = 11$) of the prognostic value of the GPS/mGPS, in cancer patients receiving chemo/radiotherapy ($n > 1500$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
Forrest et al.[13]	Glasgow, UK	Lung (NSCLC)	109	1.9 (<0.01)	GPS predicted survival independent of ECOG-ps/platinum therapy
Crumley et al.,[47]	Glasgow, UK	Gastro-oesophageal	65	1.7 (<0.05)	mGPS predicted survival independent of ECOG-ps/platinum therapy
Kobayashi et al.[48]	Tokyo, Japan	Oesophageal	48	5.9 (<0.01)	GPS predicted toxicity in patients receiving neoadjuvant therapy
Sharma et al.[49]	London/Sydney	Colorectal	52	NR	GPS predicted toxicity and survival independent of stage/treatment
Ishizuka et al.[50]	Tochigi, Japan	Colorectal	112	6.0 (<0.01)	GPS predicted survival in patients receiving adjuvant therapy
Wang et al.[51]	Kaohsiung, Taiwan	Oesophageal	123	3.4 (<0.001)	GPS predicted survival in patients receiving radiotherapy
Roxburgh et al.[52]	Glasgow, UK	Colon	348	3.2 (<0.01)	mGPS predicted survival in patients receiving adjuvant therapy
Chau et al.[53]	Sydney, Australia	Various	68	4.1 (<0.01)	GPS predicted survival in patients receiving docetaxel
Hwang et al.[54]	Gwangui, South Korea	Gastric	402	1.8 (<0.01)	GPS predicted survival independent of performance status
Morimoto et al.[55]	Yokohama, Japan	Hepatocellular	81	5.5 (<0.001)	GPS predicted survival in patients receiving sorafenib
Gioulbasanis et al.[56]	Heraklion, Greece	Lung (metastatic)	96	1.9 (<0.01)	GPS) predicts toxicity and efficacy in platinum-based treatment

HR, multivariate hazard ratio for incremental change of GPS; NR, not reported.

Table 5
Studies ($n = 11$) of the prognostic value of the GPS/mGPS, in patients with inoperable cancer ($n > 2000$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
Forrest et al.[57]	Glasgow, UK	Lung (NSCLC)	109	1.7 (<0.001)	GPS predicted survival independent of ECOG-ps/stage/treatment
Al Murri et al.[58]	Glasgow, UK	Breast	96	2.3 (<0.001)	GPS predicted survival independent of stage/treatment
Crumley et al.[59]	Glasgow, UK	Gastro-oesophageal	258	1.5 (<0.001)	GPS predicted survival independent of stage/treatment
Glen et al.[60]	Glasgow, UK	Pancreas	187	1.7 (<0.001)	GPS predicted survival independent of stage
Read et al.[61]	Sydney, Australia	Colorectal	84	2.3 (<0.05)	GPS independent of stage/treatment
Ramsey et al.[62]	Glasgow, UK	Renal	119	2.4 (<0.001)	GPS predicted survival independent of scoring systems
Sharma et al.[63]	Sydney, Australia	Ovarian	154	1.7 (<0.01)	GPS independent of stage/treatment
Pinato et al.[64]	London, UK	Lung (mesothelioma)	171	2.6 (<0.001)	mGPS predicted survival independent of NLR and EPS
Leung et al.[65]	Glasgow, UK	Lung (NSCLC)	261	1.7 (<0.001)	mGPS predicted survival independent of ECOG-ps/stage/treatment
Pinato et al.[66]	London, UK	Hepatocellular	578	2.7 (<0.01)	GPS predicted survival in training and validation datasets
Partridge et al.[67]	Edinburgh, UK	5 sites	102	2.7 (<0.01)	mGPS predicted survival independent of tumour site in palliative care

HR, multivariate hazard ratio for incremental change of GPS; NR, not reported; NLR, neutrophil lymphocyte ratio; EPS, European organisation for the research and treatment of cancer Prognostic Score.

Table 6
Studies ($n = 15$) of associations with the GPS/mGPS in patients with cancer ($n > 2000$).

Study	Centre	Tumour site	n	Comments
Brown et al.[68]	Glasgow, UK	Lung and colorectal	50	GPS associated with weight loss, poor performance status and biochemical disturbance
K-Korpacka[69]	Wroclaw, Poland	Gastro-oesophageal	96	GPS associated with weight loss, transferrin, IL-1, IL-6, IL-8, TNF, VEGF-A and midkine concentrations
Leung et al.[70]	Glasgow, UK	Colorectal	106	mGPS associated with plasma retinol, lutein, lycopene, alpha and beta carotene
Kerem et al.[71]	Ankara, Turkey	Gastric	60	GPS associated with weight loss, ghrelin, resistin, adiponectin and leptin
Fujiwara et al.[72]	Tokyo, Japan	Hepatocellular	66	GPS associated with blood transfusion and post-operative complications
Meek et al.[73]	Glasgow, UK	Lung (NSCLC)	56	mGPS associated with haemoglobin and IGFBP-3
Skipworth et al.[74]	Edinburgh, UK	Gastro-oesophageal	293	mGPS associated with weight loss, dietary intake, MAMC and KPS
Shimoda et al.[75]	Tochigi, Japan	Pancreas (unresectable)	83	GPS associated with responses to treatment
Diakowska et al.[76]	Wroclaw, Poland	Gastro-oesophageal	135	GPS associated with cachexia in cancer and controls
Giannousi et al.[77]	Heraklion, Greece	Lung (metastatic)	122	GPS associated with MNA, anxiety, depression and survival
Blomberg et al.[78]	Stockholm, Sweden	ENT and non-cancer	484	Combination of C-reactive protein and albumin associated with mortality following PEG
Richards et al.[79]	Glasgow, UK	Colorectal	343	mGPS associated with tumour necrosis
Naito et al.[80]	Shizuoka, Japan	Gastro-oesophageal	47	GPS associated with clinical responses to oxycodone
Leung et al.[81]	Glasgow, UK	Colorectal	108	mGPS associated with plasma B6
Richards et al.[82]	Glasgow, UK	Colorectal	174	mGPS associated with skeletal muscle index

NSCLC, non-small cell lung cancer; MNA, mini-nutritional assessment; IGFBP-3, insulin like growth factor binding protein-3.

Imaging, Diagnosis, Prognosis

Clinical Cancer Research

Prognostic Factors in Patients with Advanced Cancer: A Comparison of Clinicopathological Factors and the Development of an Inflammation-Based Prognostic System

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Clin Cancer Res; 19(19); 5456–64.

Glasgow prognostic score

Biomarkers

CRP and albumin were used as biomarkers of the inflammatory response and were taken by venous blood sampling at entry points to both studies. The limit of detection of CRP was less than 5mg/L, all samples (CRP and albumin) were analyzed at a central laboratory. The mGPS was calculated as follows:

- CRP $\leq$ 10mg/L = 0
- CRP > 10mg/L = 1
- CRP > 10mg/L and albumin < 35 g/L = 2

Table 1. Patient demographics—test sample and validation sample

Parameter	Test sample ($n = 1825$) n (%)	Validation sample ($n = 631$) n (%)
Age (≤65/65- 74/≥74 years)	1,014/509/302 (56/28/16)	368/148/115 (58/24/18)
Sex (M/F)	931/894 (51/49)	237/294 (53/47)
Country[a]		
Switzerland	109 (6)	61 (10)
Germany	248 (14)	0 (0)
Denmark	12 (1)	0 (0)
Australia	0 (0)	11 (2)
United Kingdom	284 (16)	52 (18)
Iceland	150 (8)	0 (0)
Austria	0 (0)	80 (13)
Italy	348 (19)	0 (0)
Norway	541 (30)	426 (68)
Sweden	133 (7)	0 (0)
Canada	0 (0)	1 (1)
Primary cancer site		
Breast	244 (13)	88 (14)
Urological	124 (7)	43 (7)
Gynaecologic	138 (8)	14 (2)
Prostate	223 (12)	69 (11)
Gastrointestinal	387 (21)	183 (29)
Haematologic	107 (6)	23 (4)
Head and Neck	90 (5)	15 (2)
Pulmonary	310 (17)	117 (19)
Others	202 (11)	79 (13)
Place of care		
Inpatient	1,510 (83)	437 (69)
Outpatient	315 (17)	194 (31)

[a]Where $n = 0$, study not recruiting in that country.

Table 2. The relationship between clinicopathological factors and survival in patients with advanced cancer—test sample ($n = 1,825$) and validation sample ($n = 631$)

	Test sample					Validation sample				
		Univariate[b]		Multivariate[b]			Univariate[b]		Multivariate[b]	
	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≤65/65–74/≥74)	1,014/509/302	1.13 (1.05–1.21)	0.001			368/148/115	1.01 (0.88–1.14)	0.987		
Sex (male/female)	931/894	0.93 (0.82–1.06)	0.270			337/294	0.91 (0.73–1.14)	0.417		
Symptoms (EORTC QLQ-C30)[a]										
Cognitive function	1,529	0.96 (0.93–0.98)	<0.001			631	0.99 (0.99–1.00)	0.067		
Dyspnea	1,528	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.04)	0.002	631	1.01 (0.99–1.04)	0.565		
Appetite loss	1,531	1.02 (1.01–1.04)	0.002			631	1.00 (0.99–1.04)	0.836		
Quality of life	1,513	0.94(0.92–0.97)	<0.001			631	0.99 (0.99–1.00)	0.043	0.99 (0.99–0.99)	0.011
Physical functioning	1,533	0.89 (0.87–0.91)	<0.001			631	1.00 (0.99–1.03)	0.005	0.99 (0.98–1.00)	<0.001
Role functioning	1,525	0.93 (0.91–0.96)	<0.001			631	1.00 (0.99–1.03)	0.443		
Emotional functioning	1,528	0.98 (0.96–1.01)	0.157			631	1.06 (1.00–1.10)	0.042		
Social functioning	1,524	0.99 (0.97–1.01)	0.235			631	1.01 (1.01–1.05)	0.512		
Fatigue	1,531	1.05 (1.03–1.07)	<0.001			631	1.00 (0.99–1.04)	0.533		
Nausea and vomiting	1,537	1.01 (0.99–1.03)	0.237			631	1.04 (1.00–1.08)	0.118		
Pain	1,535	1.01 (0.99–1.03)	0.314			631	1.05 (1.01–1.08)	0.012	1.04 (1.00–1.09)	0.028
Insomnia	1,530	0.99 (0.98–1.01)	0.453			631	1.00 (0.99–1.02)	0.387		
Constipation	1,524	1.00 (0.98–1.01)	0.654			631	1.00 (0.99–1.00)	0.636		
Diarrhea	1,521	0.99 (0.97–1.01)	0.373			631	1.00 (0.99–1.00)	0.056		
BMI (<20/≥20)[c]	376/1403	0.84 (0.74–0.95)	0.007			104/527	0.73 (0.57–0.94)	0.015	0.76 (0.60–0.98)	0.031
Performance status (ECOG grouping)[d]										
P1 (ECOG 2)	713	1.21 (1.05–1.40)	0.007			262	1.58 (1.27–1.97)	<0.001		
P2 (ECOG 3)	549	1.98 (1.71–2.29)	<0.001	1.76 (1.50–2.06)	<0.001	83	3.74 (2.78–5.02)	<0.001	2.12 (1.48–3.04)	<0.001
P3 (ECOG 4)	179	3.61 (2.97–4.39)	<0.001	2.77 (2.17–3.52)	<0.001	13	3.75 (2.03–6.91)	<0.001		
mGPS[d]										
G1 (mGPS 1)	544	1.55 (1.32–1.84)	<0.001	1.62 (1.35–1.93)	<0.001	168	1.76 (1.39–2.22)	<0.001	1.58 (1.25–2.01)	<0.001
G_2 (mGPS 2)	1,004	2.01 (1.71–2.35)	<0.001	2.05 (1.72–2.44)	<0.001	177	2.41 (1.90–3.05)	<0.001	2.06 (1.62–2.63)	<0.001

[a]EORTC QLQ-C30 scores available on approximately 1,500 patients in test sample.

[b]HR expressed as per 10 unit change.

[c]BMI available on 1,779 patients in test sample.

[d]Using indicator variables.

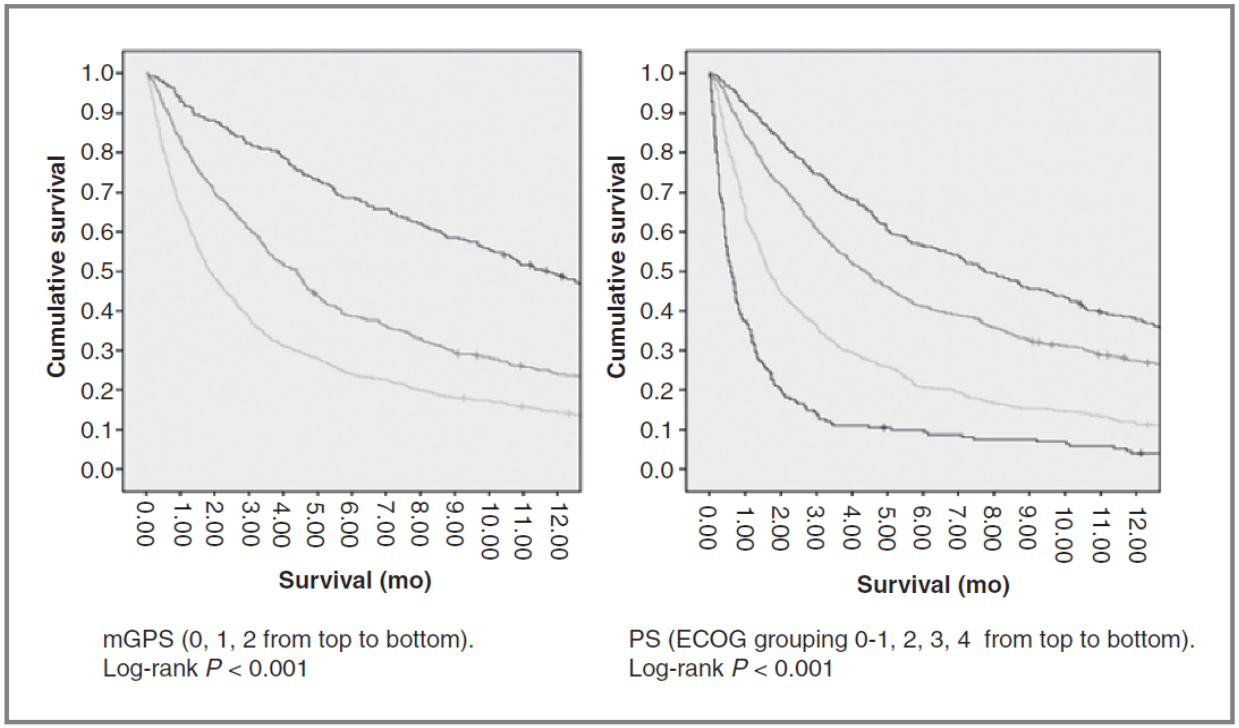

Figure 1. Kaplan–Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Test sample ($n = 1,825$). Both mGPS and performance status predict survival $P < 0.001$.

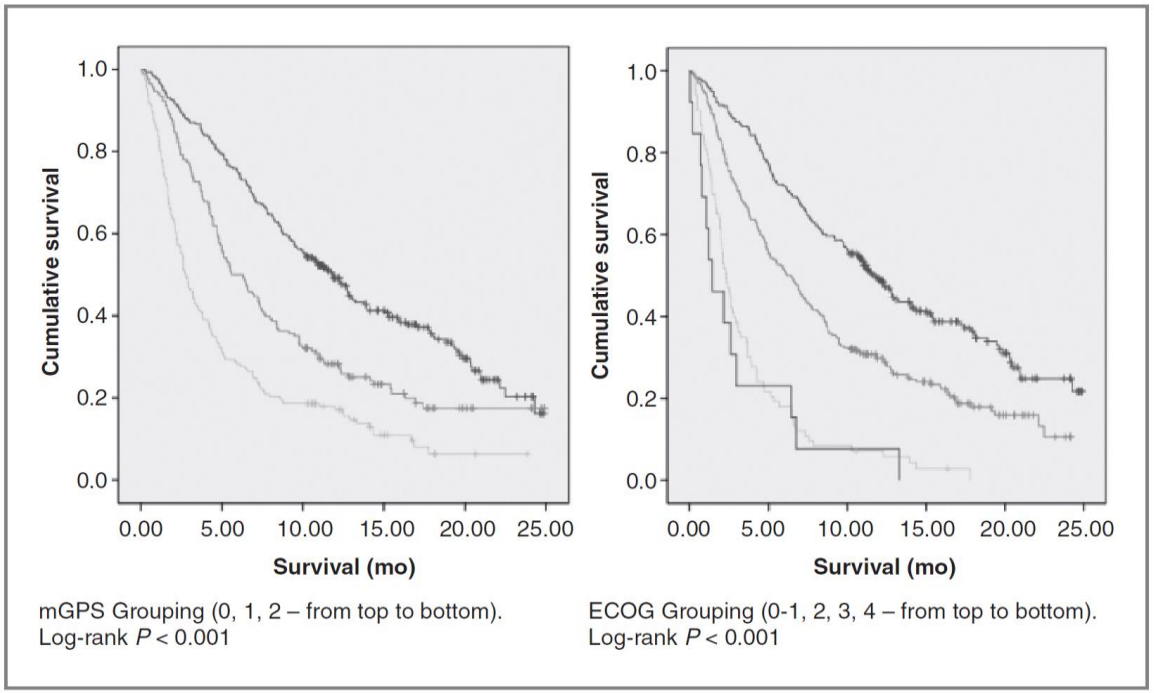

Figure 2. Kaplan–Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Validation sample ($n = 631$). Both mGPS and performance status predict survival $P < 0.001$.

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A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study

Michael J. Proctor [a,*], *David S. Morrison* [d], *Dinesh Talwar* [b], *Steven M. Balmer* [b], *Colin D. Fletcher* [b], *Denis St.J. O'Reilly* [b], *Alan K. Foulis* [c], *Paul G. Horgan* [a], *Donald C. McMillan* [a]

Introduction: Components of the systemic inflammatory response, combined to form inflammation-based prognostic scores (modified Glasgow Prognostic Score (mGPS), Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Prognostic Index (PI), Prognostic Nutritional Index (PNI)) have been associated with cancer specific survival. The aim of the present study was to compare the prognostic value of these scores.

Table 1 – Systemic inflammation-based prognostic scores.

The modified Glasgow Prognostic Score	Score
C-reactive protein $\leqslant$ 10 mg/l and albumin $\geqslant$ 35 g/l	0
C-reactive protein $\leqslant$ 10 mg/l and albumin < 35 g/l	0
C-reactive protein > 10 mg/l	1
C-reactive protein > 10 mg/l and albumin < 35 g/l	2
Neutrophil Lymphocyte Ratio	
Neutrophil count:lymphocyte count < 5:1	0
Neutrophil count:lymphocyte count $\geqslant$ 5:1	1
Platelet Lymphocyte Ratio	
Platelet count:lymphocyte count < 150:1	0
Platelet count:lymphocyte count 150–300:1	1
Platelet count:lymphocyte count > 300:1	2
Prognostic Index	
C-reactive protein $\leqslant$ 10 mg/l and white cell count $\leqslant 11 \times 10^9$/l	0
C-reactive protein $\leqslant$ 10 mg/l and white cell count > 11×10^9/l	1
C-reactive protein > 10 mg/l and white cell count $\leqslant 11 \times 10^9$/l	1
C-reactive protein > 10 mg/l and white cell count > 11×10^9/l	2
Prognostic Nutritional Index	
Albumin (g/L) + 5 × total lymphocyte count × 10^9/l $\geqslant$ 45	0
Albumin (g/L) + 5 × total lymphocyte count × 10^9/l < 45	1

Table 2 – The relationship between patient characteristics, tumour site, inflammatory-based prognostic scores and survival.

			Patients $n = 8759$ (%)	Five year overall survival % (n of deaths) $n = 5163$	p-Value	Five year cancer specific survival % (n of deaths) $n = 4417$	p-Value
Age	⩽65 years		4237 (48)	52 (1977)	<0.001	55 (1808)	<0.001
	65–74 years		2620 (30)	33 (1703)		41 (1439)	
	⩾75 years		1902 (22)	21 (1483)		31 (1170)	
Sex	Male		4115 (47)	29 (2844)	<0.001	36 (2432)	<0.001
	Female		4644 (53)	49 (2319)		55 (1985)	
SIMD 2006	1 (least deprived)		1278 (15)	51 (609)	<0.001	57 (523)	<0.001
	2		1138 (13)	48 (579)		54 (495)	
	3		1391 (16)	43 (779)		48 (683)	
	4		1786 (20)	37 (1110)		44 (940)	
	5 (most deprived)		3166 (36)	33 (2086)		40 (1776)	
Tumour site	Breast		1853 (21)	79 (361)	<0.001	85 (263)	<0.001
	Bladder		437 (5)	48 (226)		63 (149)	
	Gynaecological		460 (5)	45 (248)		51 (217)	
	Prostate		456 (5)	53 (206)		64 (153)	
	Gastroesophageal		874 (10)	12 (754)		15 (697)	
	Haematological		817 (10)	48 (418)		57 (320)	
	Renal		400 (5)	38 (242)		44 (214)	
	Colorectal		996 (11)	39 (583)		45 (493)	
	Head and neck		555 (7)	34 (344)		51 (239)	
	Hepatopancreaticobiliary		474 (5)	7 (430)		8 (410)	
	Pulmonary		1437 (16)	5 (1351)		7 (1262)	
Inflammation based prognostic scores	mGPS	0	3673 (42)	61 (1349)	<0.001	68 (1083)	<0.001
		1	2436 (28)	32 (1640)		39 (1425)	
		2	2650 (30)	16 (2174)		22 (1909)	
	NLR	0	5151 (59)	51 (2401)	<0.001	58 (2021)	<0.001
		1	3608 (41)	23 (2762)		29 (2396)	
	PLR	0	2734 (31)	52 (1253)	<0.001	60 (996)	<0.001
		1	3522 (40)	42 (1993)		48 (1716)	
		2	2503 (29)	23 (1917)		28 (1705)	
	PI	0	3084 (35)	64 (1042)	<0.001	70 (832)	<0.001
		1	3460 (40)	31 (2303)		38 (1994)	
		2	2215 (25)	17 (1818)		23 (1591)	
	PNI	0	4342 (50)	57 (1806)	<0.001	63 (1487)	<0.001
		1	4417 (50)	21 (3357)		27 (2930)	

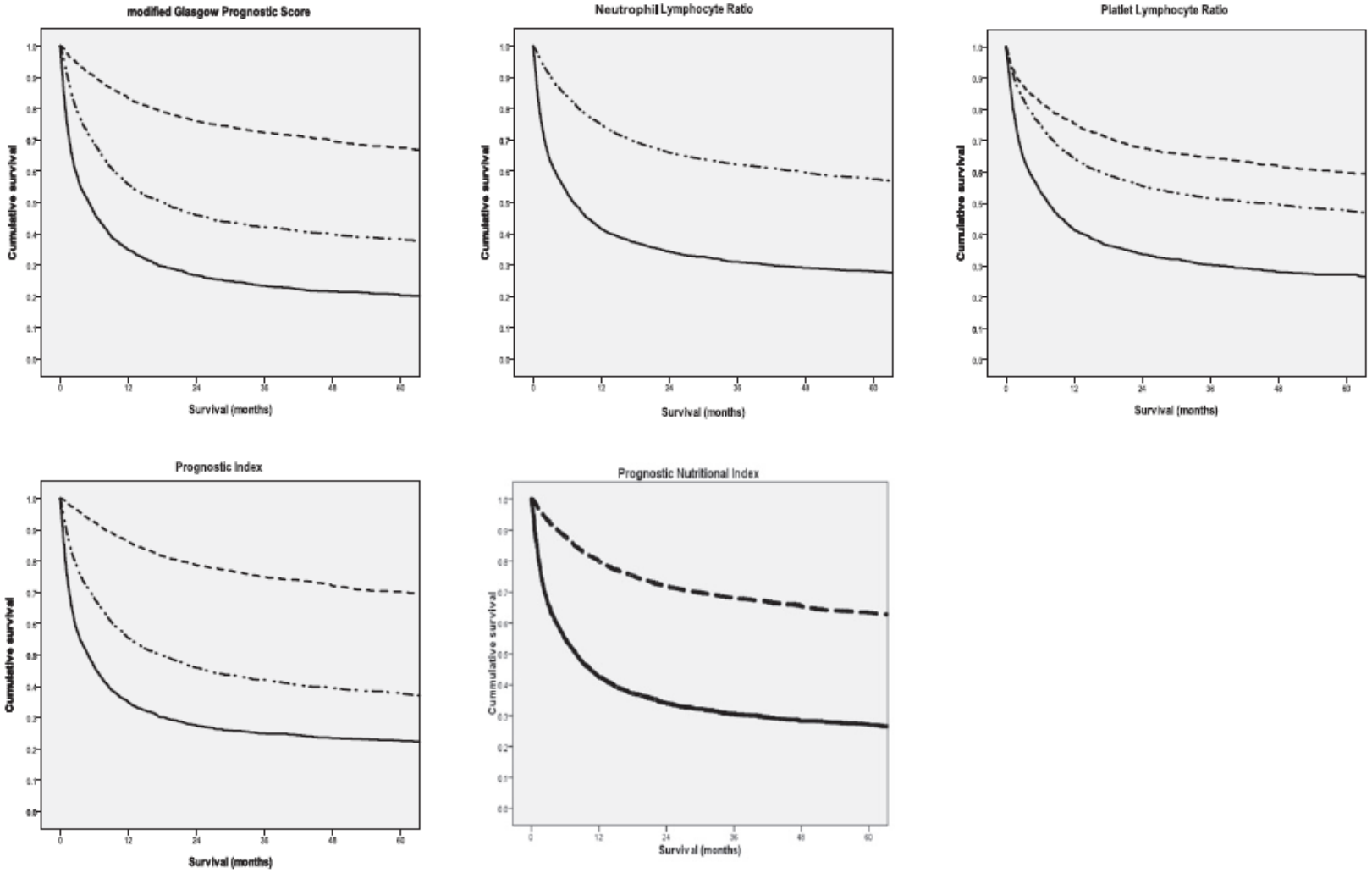

Fig. 1 – The relationship between the mGPS (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), NLR (0-top, large dash line; 1-bottom, solid line), PLR (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PI (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PNI (0-top, large dash line; 1-bottom, solid line) and cancer specific survival in all patients (all $p<0.001$).

Table 3 – The relationship between inflammation-based prognostic scores and survival. Adjusted for age, sex, deprivation and stratified by tumour site.

		Overall survival		Cancer specific survival	
		HR	*p*-Value	HR	*p*-Value
All patients (n = 8759)					
mGPS	0	1	<0.001	1	<0.001
	1	1.74	<0.001	1.85	<0.001
	2	2.91	<0.001	3.06	<0.001
NLR	0	1	<0.001	1	<0.001
	1	1.93	<0.001	1.97	<0.001
PLR	0	1	<0.001	1	<0.001
	1	1.22	<0.001	1.31	<0.001
	2	1.89	<0.001	2.08	<0.001
PI	0	1	<0.001	1	<0.001
	1	2.03	<0.001	2.15	<0.001
	2	2.87	<0.001	3.03	<0.001
PNI	0	1	<0.001	1	<0.001
	1	2.24	<0.001	2.34	<0.001
Patients sampled within two months following cancer diagnosis (n = 4674)					
mGPS	0	1	<0.001	1	<0.001
	1	1.65	<0.001	1.74	<0.001
	2	2.35	<0.001	2.44	<0.001
NLR	0	1	<0.001	1	<0.001
	1	1.76	<0.001	1.77	<0.001
PLR	0	1	<0.001	1	<0.001
	1	1.19	<0.001	1.24	<0.001
	2	1.71	<0.001	1.82	<0.001
PI	0	1	<0.001	1	<0.001
	1	1.78	<0.001	1.87	<0.001
	2	2.44	<0.001	2.51	<0.001
PNI	0	1	<0.001	1	<0.001
	1	1.98	<0.001	2.01	<0.001

Table 4 – The relationship between inflammation-based prognostic scores and survival in colorectal cancer patients sampled within two months following cancer diagnosis. Adjusted for age, sex, deprivation and Dukes stage.

$n = 374$		Overall survival		Cancer specific survival	
		HR	*p*-Value	HR	*p*-Value
mGPS	0	1	<0.001	1	<0.001
	1	1.81	0.004	1.91	<0.001
	2	2.30	<0.001	2.51	<0.001
NLR	0	1	0.102	1	0.146
	1	1.27	0.102	1.25	0.146
PLR	0	1	0.786	1	0.560
	1	1.16	0.487	1.30	0.281
	2	1.13	0.596	1.23	0.403
PI	0	1	<0.001	1	<0.001
	1	1.69	0.012	1.92	<0.001
	2	2.83	<0.001	3.07	<0.001
PNI	0	1	0.059	1	0.095
	1	1.33	0.059	1.31	0.095

In summary, the results of the present study show that systemic inflammation-based scores mGPS, NLR, PLR, PI and PNI have prognostic value in a variety of cancers. However, in terms of differentiating good from poor prognostic groups in a variety of tumour sites and the existing validated literature, the mGPS is superior. A measurement of systemic inflammation, in particular the mGPS, should be included in the routine assessment of all patients with cancer.

The predictive value of pre-treatment inflammatory markers in advanced non-small-cell lung cancer

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TABLE I Definition of the prognostic index (PI)

PI	*C-Reactive protein*	*White blood cells*
0	≤10 mg/L	$\leq 11 \times 10^9$
1	≤10 mg/L	$> 11 \times 10^9$
1	>10 mg/L	$\leq 11 \times 10^9$
2	>10 mg/L	$> 11 \times 10^9$

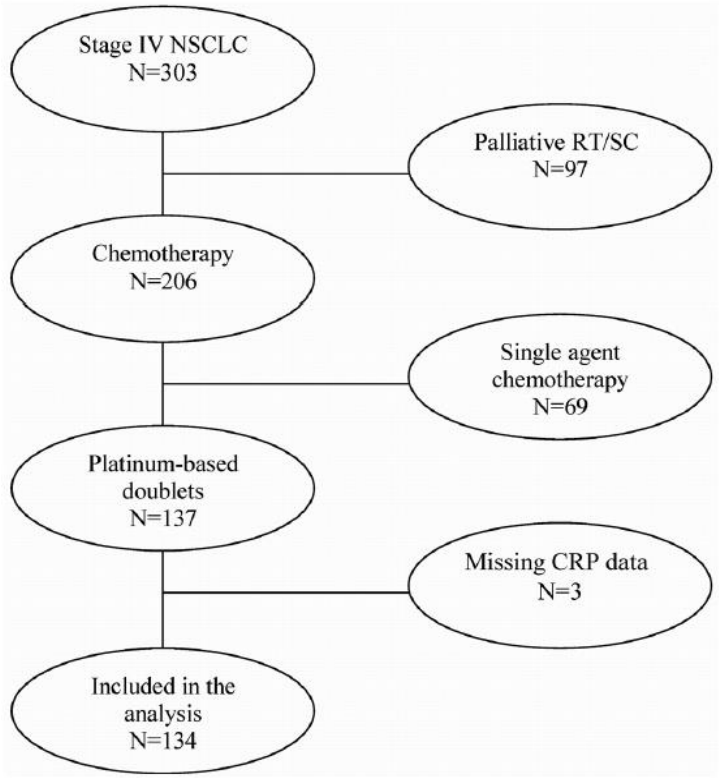

FIGURE 1 *Cohort organization chart.* NSCLC = *non-small-cell lung cancer;* RT = *radiotherapy;* SC = *supportive care;* CRP = *C-reactive protein.*

TABLE II Clinical characteristics of the study patients

Characteristic	*Patients*	
	(n)	*(%)*
Sex		
Male	71	53
Female	63	47
Smoking status		
Smoker	40	30
Ex-smoker	65	48
Never-smoker	29	22
ECOG performance status		
0–1	116	87
2	18	13
Tumour type		
Adenocarcinoma	96	72
Squamous cell carcinoma	13	10
Other	25	18
Stage		
IV (pleural effusion)	15	11
IV	119	89
Chemotherapy type		
Carboplatin–gemcitabine	71	53
Carboplatin–paclitaxel	46	34
Other platinum-based doublets	17	13
Weight loss		
<5%	86	64
≥5%	48	36

ECOG = Eastern Cooperative Oncology Group.

TABLE III Clinical difference among the prognostic index (PI) groups

Characteristic	*Patients by PI group (n)*			p *Value*
	0	*1*	*2*	*(Spearman*
	(N=46)	*(N=60)*	*(N=28)*	*correlation)*
Age				
<65	30	34	20	0.336
≥65	16	26	8	
Smoking				
Smoker or ex-smoker	30	13	0	0.002
Never-smoker	16	47	28	
ECOG performance status				
0–1	43	51	22	0.060
2	3	9	6	
Sex				
Female	28	26	9	0.013
Male	18	34	19	
Weight loss				
<5%	36	37	13	0.019
≥5%	10	23	15	

ECOG = Eastern Cooperative Oncology Group.

TABLE V Factors affecting rate of progression

Variable	*Coefficient*	*p Value*
Constant[a]	0.26	0.002
Age	0.47	0.09
Sex	1.37	0.45
Weight loss	1.11	0.81
Smoking status	0.61	0.30
ECOG performance status	2.58	0.09
Prognostic index	1.79	0.04

[a] *y* intercept.
ECOG = Eastern Cooperative Oncology Group.

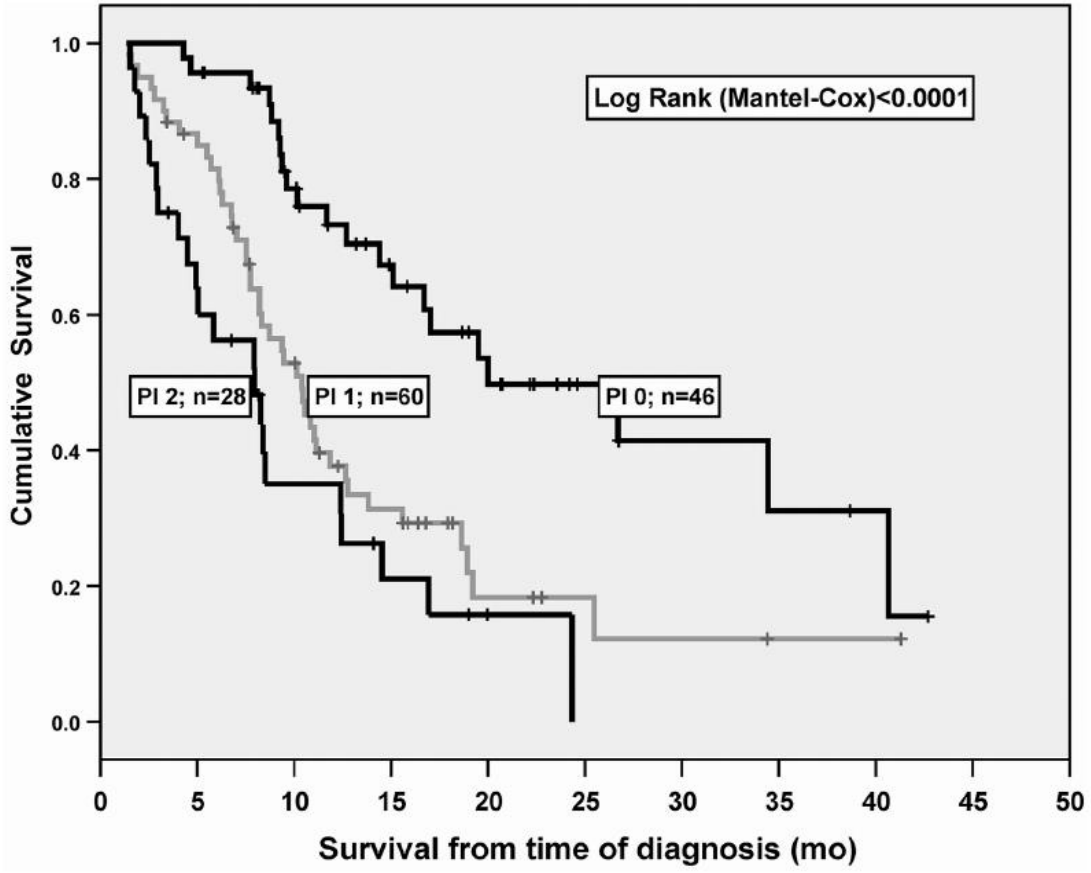

FIGURE 2 *Kaplan–Meier survival curves based on the prognostic index (PI).*

Marqueurs circulants de l'inflammation

Annals of Oncology 24: 2073–2079, 2013
doi:10.1093/annonc/mdt175
Published online 16 May 2013

Circulating levels of immune and inflammatory markers and long versus short survival in early-stage lung cancer

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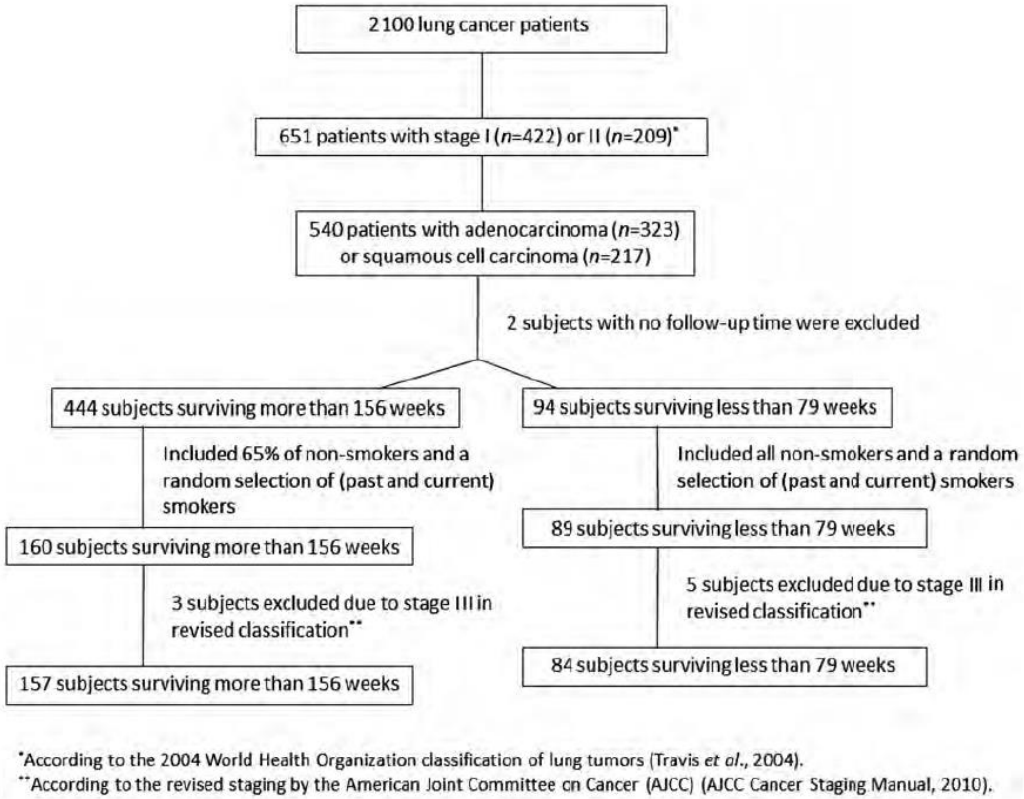


Figure 1. Flow diagram of study participants.

Table 1. Distribution of characteristics of lung cancer patients by survival status.

Characteristics	LS (>156 weeks) ($n = 157$)	SS (<79 weeks) ($n = 84$)
Median follow-up time (weeks), (IQR)	341.0 (289.4–389.1)	44.6 (20.6–61.3)
Age (years), *n* (%)		
<65	56 (35.7)	20 (23.8)
65 to <70	41 (26.1)	16 (19.0)
70 to <75	44 (28.0)	20 (23.8)
≥75	16 (10.2)	28 (33.3)
Sex, *n* (%)		
Males	123 (78.3)	68 (81.0)
Females	34 (21.7)	16 (19.0)
Stage[a], *n* (%)		
IA	43 (27.4)	16 (19.0)
IB	38 (24.2)	26 (31.0)
IIA	51 (32.5)	17 (20.2)
IIB	25 (15.9)	25 (29.8)
Histology, *n* (%)		
Adenocarcinoma	89 (56.7)	46 (54.8)
Squamous cell carcinoma	68 (43.3)	38 (45.2)
Smoking status, *n* (%)		
Never smoker	22 (14.0)	5 (6.0)
Former smoker	73 (46.5)	38 (45.2)
Current smoker	62 (39.5)	41 (48.8)
COPD (self-reported), *n* (%)		
No	113 (75.8)	52 (71.2)
Yes	36 (24.2)	21 (28.8)
COPD (spirometer-based), *n* (%)		
Normal or mild	81 (81.0)	28 (57.1)
Moderate or severe	19 (19.0)	21 (42.9)
Surgery, *n* (%)		
No	5 (3.2)	13 (15.5)
Yes	152 (96.8)	71 (84.5)
Chemotherapy treatment, *n* (%)		
No	111 (70.7)	55 (65.5)
Yes	46 (29.3)	29 (34.5)
Radiation treatment, *n* (%)		
No	119 (76.3)	59 (72.0)
Yes	37 (23.7)	23 (28.0)

Percentages might not add up to 100% because of rounding.
Patients treated according to standard practice at clinical site where they were seen; details of chemotherapy regimens not known.
LS, long survivors; SS, short survivors; IQR, interquartile range.
[a]Staging according to the 2010 classification for lung cancer (AJCC Cancer Staging Manual. 7 edn. New York: Springer-Verlag; 2010).

Table 2. Adjusted analysis for the associations between inflammatory circulating markers and survival status[a].

Markers	Median			Q2 versus Q1		Q3 versus Q1		Q4 versus Q1		P^{c}_{trend}	Q-value[d]
	LS	SS	P-value*	OR[b]	(95% CI)	OR[b]	(95% CI)	OR[b]	(95% CI)		
CCL15	1957.03	2317.34	2.8×10^{-4}	2.60	(1.02–6.66)	3.82	(1.48–9.88)	4.93	(1.9–12.8)	7.4×10^{-4}	0.042
IL-8	7.30	9.77	0.002	0.62	(0.24–1.57)	1.41	(0.59–3.35)	3.05	(1.31–7.1)	0.002	0.064
CRP[e]	25 256 000.00	66 605 000.00	0.007	0.98	(0.38–2.5)	2.72	(1.17–6.31)	3.08	(1.17–8.08)	0.004	0.071
IL-2Ra	3.20	6.25	0.020	–	–	1.12	(0.52–2.43)	2.58	(1.26–5.29)	0.023	0.249
TNF-a	8.56	9.44	0.007	1.72	(0.73–4.02)	1.27	(0.53–3.09)	2.92	(1.25–6.78)	0.029	0.249
IL-6	4.51	5.64	0.048	2.48	(0.95–6.47)	3.78	(1.45–9.83)	2.84	(1.08–7.43)	0.030	0.249
TRAIL	21.52	16.53	0.085	1.04	(0.46–2.34)	0.74	(0.32–1.71)	0.38	(0.15–0.95)	0.031	0.249
IL-6R	15 793.15	16 987.09	0.034	1.04	(0.43–2.48)	1.68	(0.72–3.93)	2.07	(0.91–4.75)	0.049	0.326
CXCL13	24.59	30.04	0.001	0.92	(0.39–2.21)	1.07	(0.46–2.53)	2.25	(0.97–5.24)	0.052	0.326
TNFRII	5369.65	6910.59	0.006	0.95	(0.38–2.36)	1.44	(0.6–3.49)	2.08	(0.86–5.05)	0.060	0.341
CCL19	59.72	67.90	0.031	1.14	(0.49–2.66)	1.21	(0.51–2.84)	2.02	(0.87–4.67)	0.109	0.566
G-CSF	89.84	101.34	0.219	1.07	(0.46–2.48)	1.08	(0.45–2.56)	1.89	(0.84–4.27)	0.136	0.645
TNFRI	1234.41	1377.58	0.009	2.01	(0.83–4.89)	1.64	(0.67–4.04)	2.13	(0.87–5.2)	0.167	0.700
EGFR	37 460.37	36 289.72	0.159	0.89	(0.4–1.97)	0.66	(0.29–1.5)	0.61	(0.26–1.41)	0.185	0.700
SAA[e]	48 800 000.00	142 200 000.00	0.085	1.18	(0.47–2.98)	2.77	(1.16–6.63)	1.21	(0.43–3.42)	0.197	0.700

Markers ordered from the most significant association to the least significant according to P_{trend}.
LS, long survivors; SS, short survivors.

Mécanisme

Review

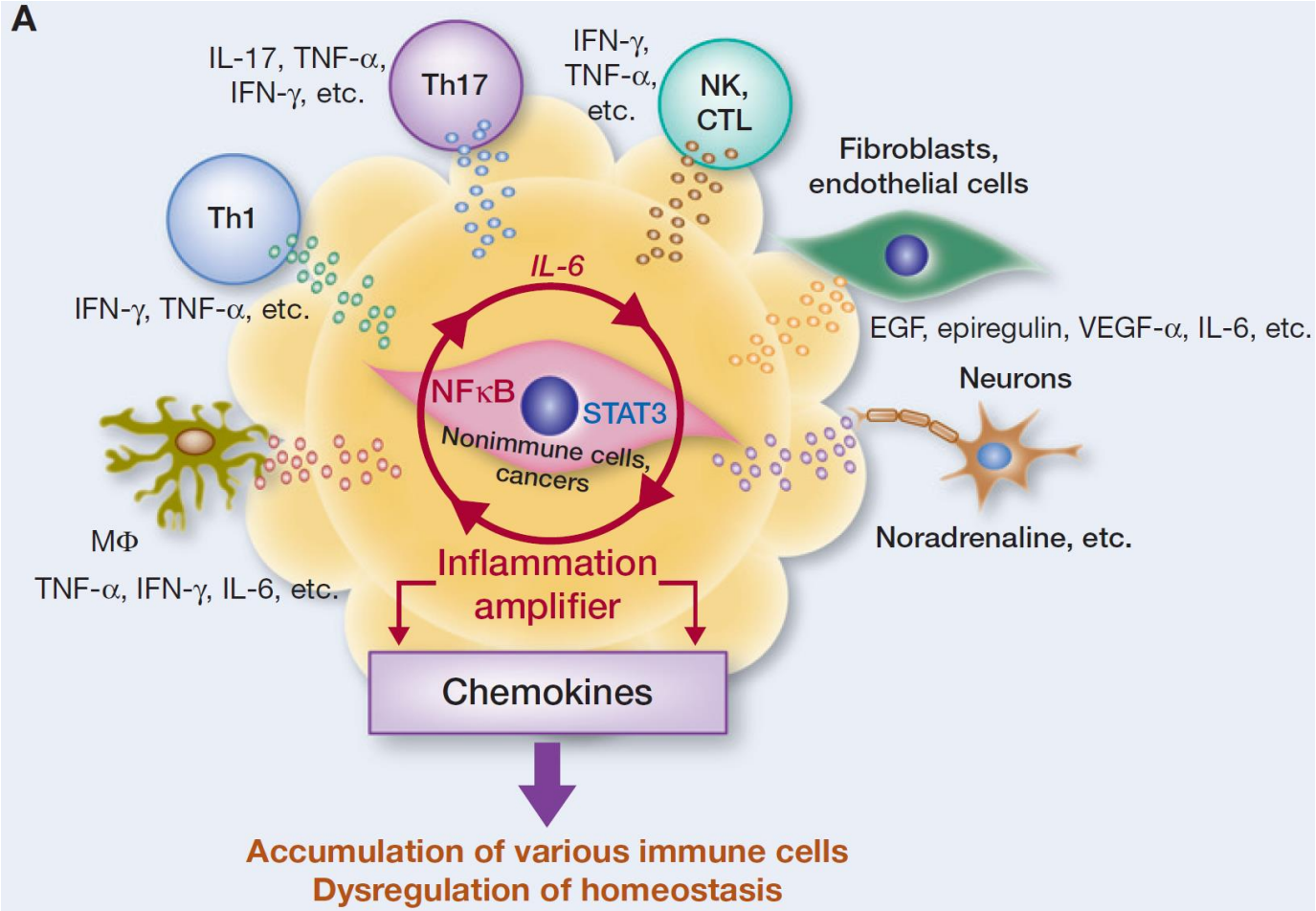
Cancer Research

Inflammation Amplifier, a New Paradigm in Cancer Biology

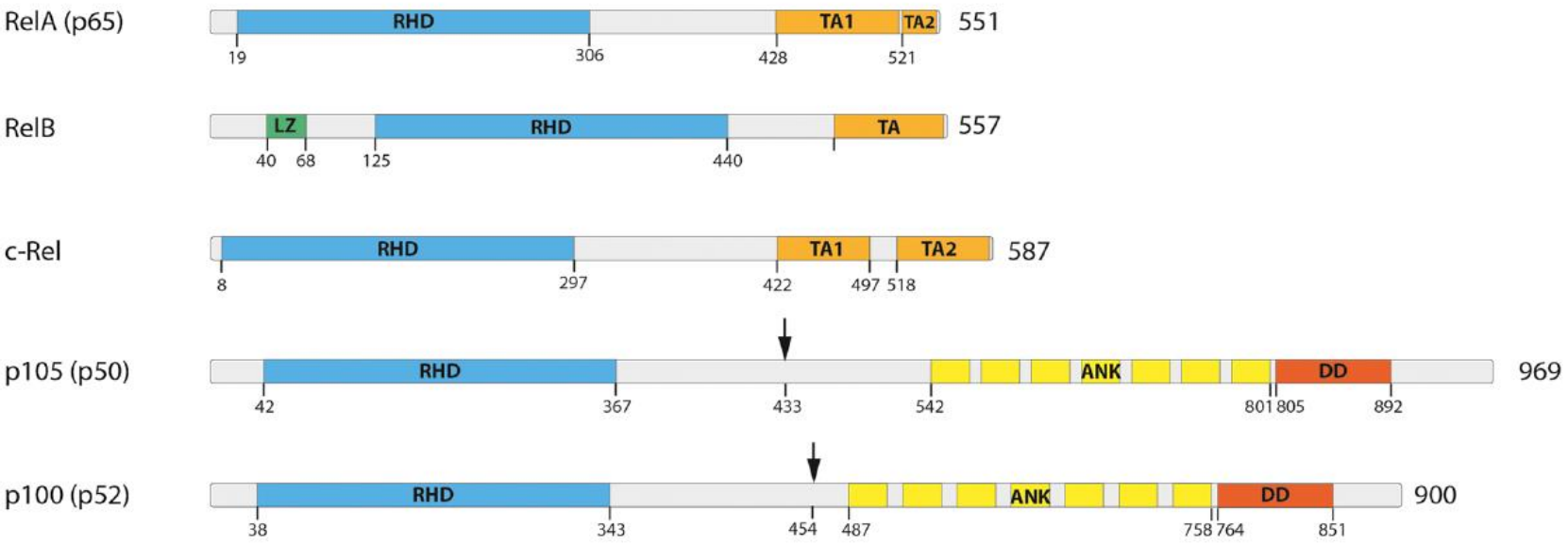
Toru Atsumi[1], Rajeev Singh[1], Lavannya Sabharwal[1], Hidenori Bando[1], Jie Meng[1], Yasunobu Arima[1], Moe Yamada[1], Masaya Harada[1], Jing-Jing Jiang[1], Daisuke Kamimura[1], Hideki Ogura[1], Toshio Hirano[2], and Masaaki Murakami[1]

Abstract

Tumor-associated inflammation can induce various molecules expressed from the tumors themselves or surrounding cells to create a microenvironment that potentially promotes cancer development. Inflammation, particularly chronic inflammation, is often linked to cancer development, even though its evolutionary role should impair nonself objects including tumors. The inflammation amplifier, a hyperinducer of chemokines in nonimmune cells, is the principal machinery for inflammation and is activated by the simultaneous stimulation of NF-κB and STAT3. We have redefined inflammation as local activation of the inflammation amplifier, which causes an accumulation of various immune cells followed by dysregulation of local homeostasis. Genes related to the inflammation amplifier have been genetically associated with various human inflammatory diseases. Here, we describe how cancer-associated genes, including interleukin (IL)-6, Ptgs2, ErbB1, Gas1, Serpine1, cMyc, and Vegf-α, are strongly enriched in genes related to the amplifier. The inflammation amplifier is activated by the stimulation of cytokines, such as TNF-α, IL-17, and IL-6, resulting in the subsequent expression of various target genes for chemokines and tumor-related genes like BCL2L11, CPNE7, FAS, HIF1-α, IL-1RAP, and SOD2. Thus, we conclude that inflammation does indeed associate with the development of cancer. The identified genes associated with the inflammation amplifier may thus make potential therapeutic targets of cancers. *Cancer Res; 74(1); 8–14. ©2013 AACR.*


A
IL-17, TNF-α, IFN-γ, etc.
Th17
IFN-γ, TNF-α, etc.
NK, CTL
Fibroblasts, endothelial cells
Th1
IFN-γ, TNF-α, etc.
IL-6
EGF, epiregulin, VEGF-α, IL-6, etc.
NFκB
STAT3
Nonimmune cells, cancers
Neurons
MΦ
TNF-α, IFN-γ, IL-6, etc.
Noradrenaline, etc.
Inflammation amplifier
Chemokines
Accumulation of various immune cells
Dysregulation of homeostasis

The five members of the NF-κB family of proteins: RelA (p65), RelB, c-Rel,NF-κB1 (p105), and NF-κB2 (p100). p105 and p100 are processed to their shorter forms p50 and p52, respectively. All members of the NF-κB family harbor an N-terminal Rel homology domain (RHD), which mediates DNA contact and homo- and heterodimerization. Three family members (RelA, RelB and c-Rel) contain C-terminal transactivation domains (TAs), which are essential for transcriptional activity



Hoesel and Schmid *Molecular Cancer* 2013, **12**:86
http://www.molecular-cancer.com/content/12/1/86

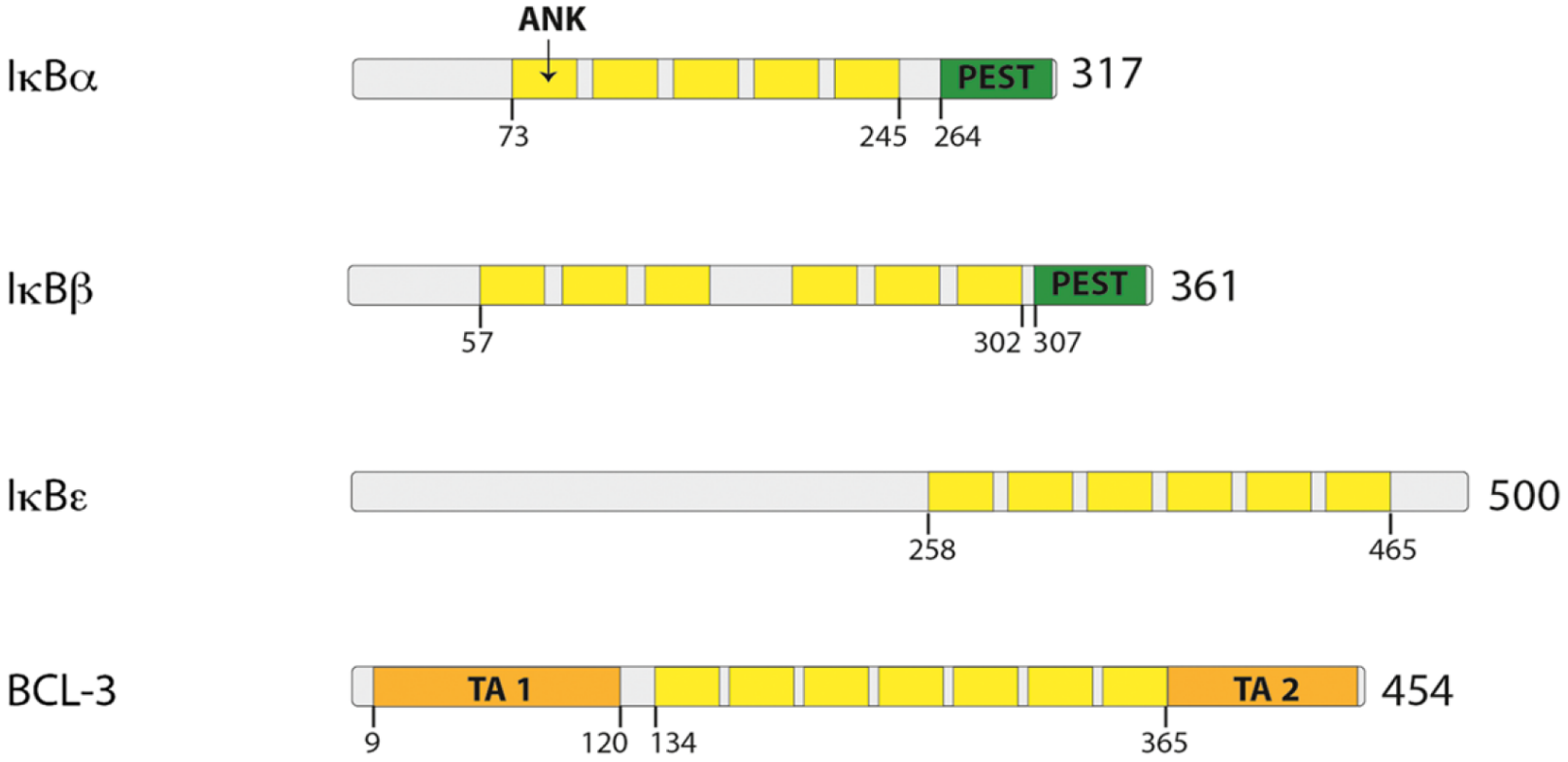
MOLECULAR CANCER

REVIEW Open Access

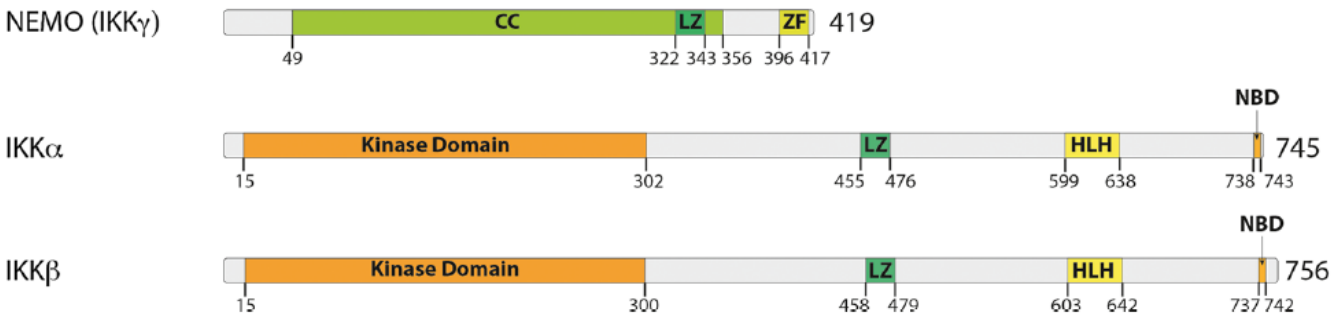
The complexity of NF-κB signaling in inflammation and cancer

Bastian Hoesel and Johannes A Schmid*

The IκB family of proteins consists of four members: IκBα, IκBβ, IκBε and BCL-3. These proteins are characterized by the presence of ankyrin (ANK) repeats, which mediate binding of IκBs to the NF-κB family of proteins. Based on the presence of ankyrin repeats, p100 and p105 can also be included into the IκB family – as their DNA-binding RHD domain is covalently linked to an IκB-like inhibitory domain. In addition to the ANK repeats IκBα and IκBβ contain PEST domains, which are enriched in proline, glutamate, serine and threonine and are required for constitutive turnover. BCL-3 differs from other IκB family members by containing TA domains, which mediate transcriptional activity when BCL-3 is associated with NF-κB dimers that bind to DNA.



The three most important members of IκB kinase (IKK) complex: NF-κB Essential Modulator (NEMO or IKKγ), IκB kinase α, (IKKα or IKK1) and IκB kinase β (IKKβ or IKK2). Further abbreviations: leucin-zipper-like motif (LZ), death domain (DD), coiled-coil domain (CC), zinc-finger domain (ZF), helix-loop-helix domain (HLH), NEMO-binding domain (NBD). It is important to note that the total number of amino acids of protein as well as the start and end of some domains can differ between publications and databases



Signaling pathways activating NF-κB

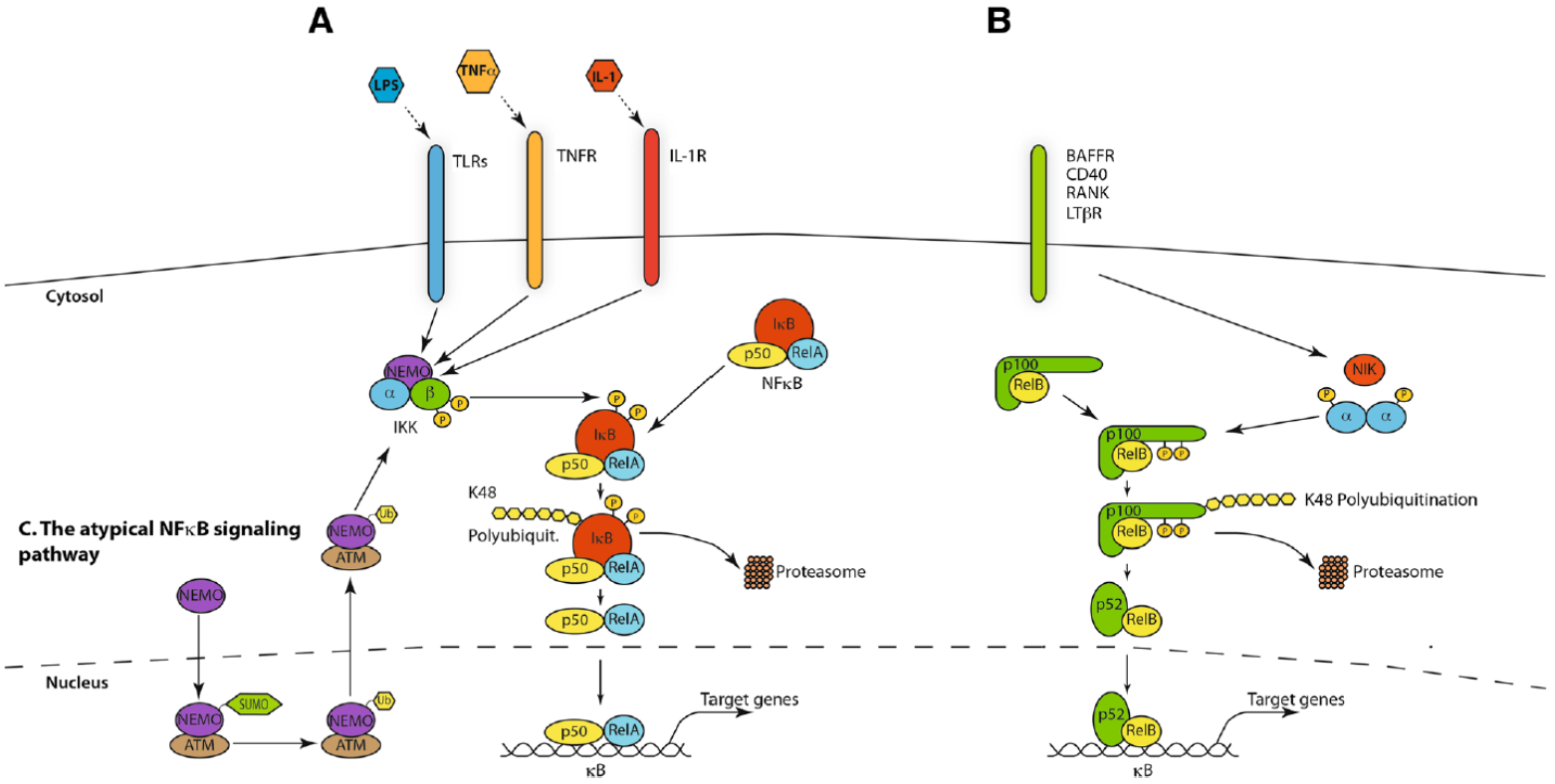


Figure 2 The canonical, non-canonical and the atypical NF-κB signaling pathway. (A) In the canonical NF-κB signaling pathway lipopolysaccharides (LPS), tumor necrosis factor α (TNFα) orinterleukin-1 (IL-1) activate Toll-like receptors (TLRs), tumor necrosis factor receptor (TNFR) and interleukin-1 receptor (IL-1R), respectively. Through a variety of adapter proteins and signaling kinases this leads to an activation of IKKβ in the IKK complex, which can then phosphorylate IκBα on Serine residues S32 and S36. This phosphorylation is a prerequisite for its subsequent polyubiquitination, which in turn results in proteasomal degradation of IκBα. NF-κB homo- or heterodimers can then translocate to nucleus and activate target gene transcription. **(B)** In the non-canonical NF-κB signaling pathway, activation of B-cell activation factor (BAFFR), CD40, receptor activator for nuclear factor kappa B (RANK) or lymphtoxin β-receptor (LTβR), leads to activation of IKKα by the NF-κB-inducing kinase (NIK). IKKα can the phosphorylate p100 on serine residues S866 and S870. This phosphorylation leads to polyubiquitination of p100 and its subsequent proteasomal processing to p52.p52-RelB heterodimers can then activate transcription of target genes. **(C)** In the atypical NF-κB signaling pathway, genotoxic stress leads to a translocation of NEMO to the nucleus where it is sumoylated and subsequently ubiquitinated. This process is mediated by the ataxia telangiectasia mutated (ATM) checkpoint kinase. NEMO and ATM can then return to the cytosol where they activate IKKβ.

Network of NF-κB interactors

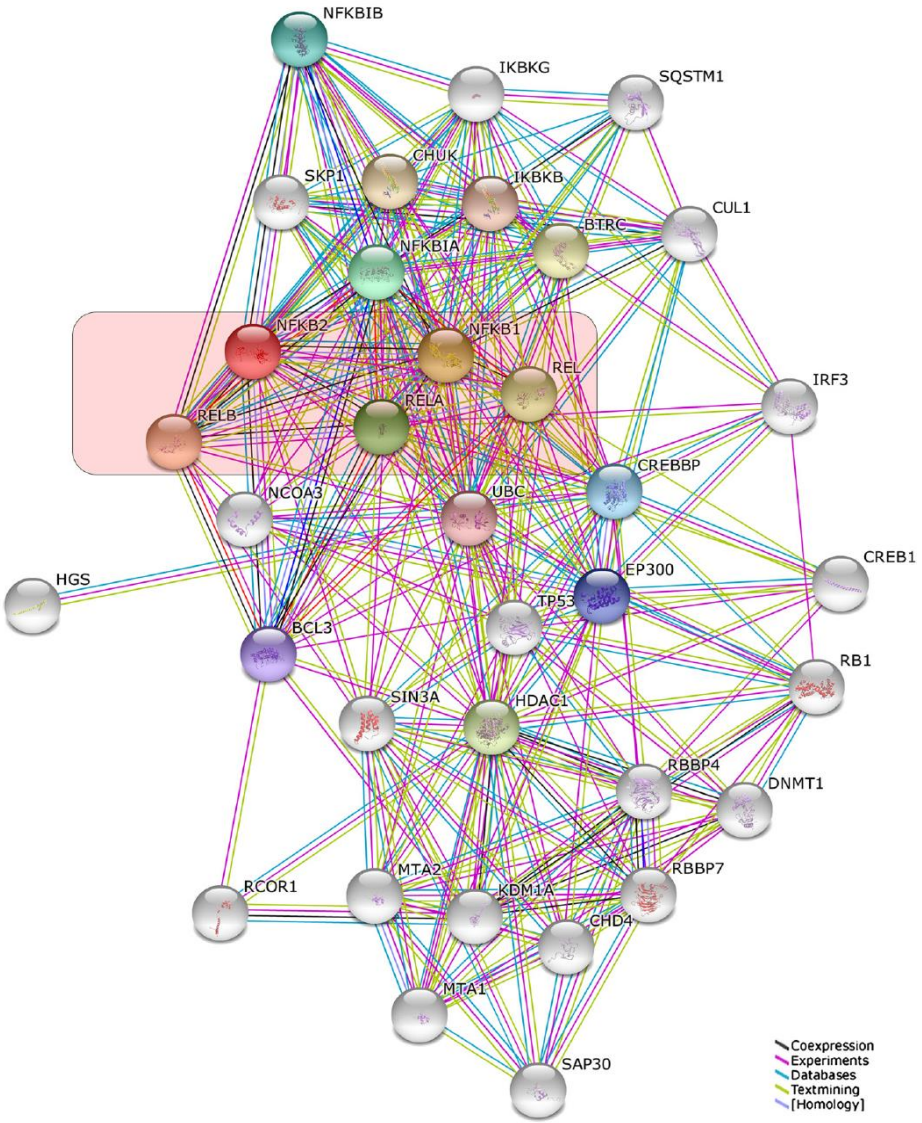
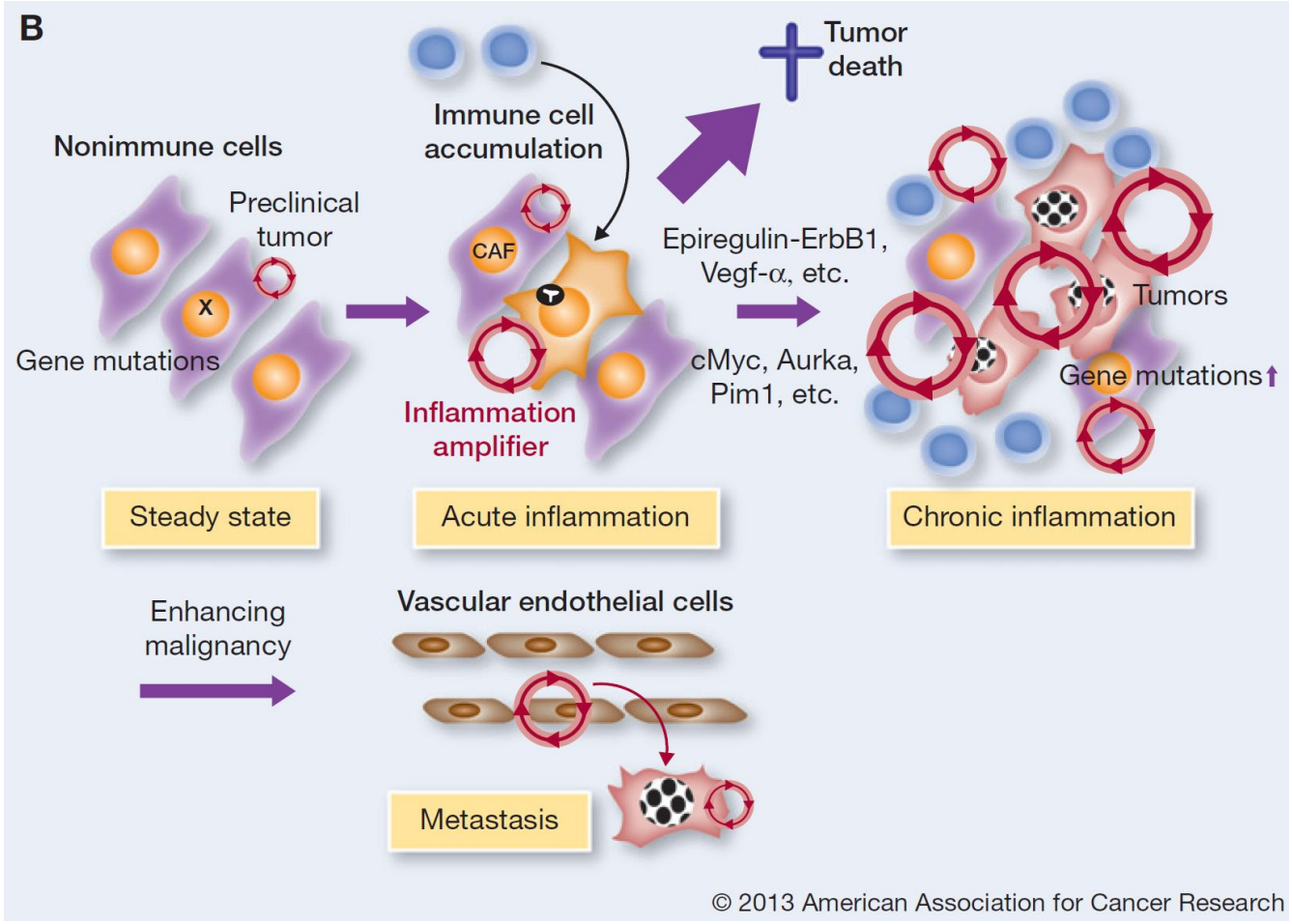


Figure 4 Network of NF-κB interactors. Evidence view of the STRING database output depicting functional and physical interactors of the NF-κB proteins, RelA, Rel (c-Rel), RelB, NFKB1 and NFKB2 obtained from: http://string-db.org/. The five NF-κB proteins are highlighted in red.


B
Tumor death
Immune cell accumulation
Nonimmune cells
Preclinical tumor
X
Gene mutations
CAF
Inflammation amplifier
Epiregulin-ErbB1, Vegf-α, etc.
cMyc, Aurka, Pim1, etc.
Tumors
Gene mutations
Steady state
Acute inflammation
Chronic inflammation
Enhancing malignancy
Vascular endothelial cells
Metastasis
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L'inflammation dans le cancer bronchique

STATE OF THE ART: CONCISE REVIEW

The Role of Inflammation in the Pathogenesis of Non-small Cell Lung Cancer

Dermot S. O'Callaghan, MD, MRCPI,† Dearbhaile O'Donnell, MD, MRCPI,**
*Finbarr O'Connell, MD, FRCPI,† and Kenneth J. O'Byrne, MD, FRCPI**

(*J Thorac Oncol.* 2010;5: 2024–2036)

TABLE 1. Studies Evaluating the Relationship Between Immune Cell Infiltrate and Prognosis in Non-small Cell Lung Cancer

Author	Study Size	Immune Cell Subtype Studied	TNM Stage	Histological Subtypes	Key Findings
Lee et al.[48]	30	T lymphocytes, plasma cells, neutrophils, macrophages	III	Sq, Ad, LC	Increased stromal lymphocyte count associated with improved survival
Tormanen-Napankangas et al.[62]	84	$CD3^+$ and $CD8^+$ T lymphocytes, B lymphocytes, macrophages	Not defined	Sq, Ad, LC	Increased intratumoral infiltration by $CD3^+$ and $CD8^+$ T lymphocytes and B lymphocytes associated with tumor cell apoptosis but not prognosis
Johnson et al.[64]	95	$CD3^+$ and $CD8^+$ T lymphocytes, B lymphocytes, NK cells, macrophages, Langerhans cells	I–III	Nonspecified NSCLC (97%), SCLC (3%)	Improved prognosis in subgroup with higher intratumoral infiltration of $CD3^+$ T lymphocytes and $S100^+$ Langerhans cells
Trojan et al.[65]	31	$CD8^+$ T lymphocytes	I–III	Sq, Ad, LC	No relationship between intratumoral lymphocyte infiltration and prognosis
Kawai et al.[66]	199	$CD8^+$ T lymphocytes, macrophages, mast cells	IV	Sq, Ad, undifferentiated NSCLC	Improved median survival times in patients with high intratumoral macrophages and $CD8^+$ T lymphocytes treated with adjuvant chemotherapy
Al-Shibli et al.[67]	335	$CD4^+$ and $CD8^+$ T lymphocytes, $CD20^+$ B lymphocytes	I–IIIA	Sq, Ad, LC	High intrastromal $CD4^+$ and $CD8^+$ lymphocyte numbers an independent prognostic factor
Hiraoka et al.[68]	109	$CD4^+$ and $CD8^+$ T lymphocytes	I–IIIA	Sq, Ad, LC, AS, carcinosarcoma[a]	High conjoint $CD4^+$ and $CD8^+$ T lymphocyte stromal infiltration a favorable prognostic factor

Wakabayashi et al.[69]	178	$CD4^+$ and $CD8^+$ T lymphocytes	I–IIIA	Sq, Ad	Higher $CD8^+$ T lymphocyte intratumoral counts associated with shorter 5-yr survival. Increased intrastromal $CD4^+$ T lymphocyte counts a favorable prognostic marker
Petersen et al.[83]	64	$CD3^+$ and $Foxp3^+$ T lymphocytes	I	Ad, Sq, "other"	Higher risk of disease recurrence with high intratumoral regulatory:total T-lymphocyte ratio
Kerr et al.[89]	95	$CD3^+$ and $CD8^+$ T lymphocytes, $CD79^+$ B lymphocytes, NK cells, macrophages, Langerhans cells	I–III[b]	Sq, Ad, AS, LC, SCLC, Car	Increased $CD3^+$ T lymphocytes, macrophages (in tumor islets only) and CD4:CD8 ratio in tumors showing histological appearances akin to regressing malignant melanoma
Takanami et al.[90]	150	NK cells	I–IIIA	Ad	NK cell infiltration (predominantly found in stromal regions) a prognostic factor in univariate analysis only
Villegas et al.[91]	50	NK cells	I–IIIA	Sq	Low numbers of intratumoral NK cells associated with increased risk of death
Welsh et al.[49]	175	Macrophages, mast cells	I–IV	Ad, Sq, "other"	High tumor islet/stromal macrophage and tumor islet/stromal mast ratios independent favorable prognostic indicators
Ohri et al.[101]	40	Macrophages		Sq, Ad, LC, "other"	Tumor islets macrophages in patients with increased 5-yr survival predominantly show a cytotoxic M1 phenotype
Kim et al.[102]	144	Macrophages	I–IV	Sq, Ad, AS, LC	High tumor islet macrophage count independent predictor of improved 5-yr survival
Takanami et al.[103]	113	Macrophages	I–IV	Ad	Greater macrophage infiltration associated with increased microvessel density and worse prognosis; macrophages predominantly identified in stroma
Zeni et al.[104]	50	Macrophages	I–IV	Sq, Ad	Increased IL-10 expression by tumor islet macrophages associated with shorter survival
Imada et al.[122]	85	Mast cells	I	Sq, Ad	Stromal mast cells correlate with angiogenesis assessed by microvessel counts and poor outcome
Tomita et al.[125]	90	Mast cells	I–IV	Ad	Increased overall mast cell infiltration associated with improved 5-yr survival rates postsurgery

Le système immunitaire dans le cancer bronchique

STATE OF THE ART: CONCISE REVIEW

The Role of Tumor-Infiltrating Immune Cells and Chronic Inflammation at the Tumor Site on Cancer Development, Progression, and Prognosis

Emphasis on Non-small Cell Lung Cancer

Roy M. Bremnes, MD, PhD,† Khalid Al-Shibli, MD, PhD,‡§ Tom Donnem, MD, PhD,*† Rafael Sirera, PhD,‖ Samer Al-Saad, MD, PhD,‡¶ Sigve Andersen, MD,*† Helge Stenvold, MD,*† Carlos Camps, MD, PhD,# and Lill-Tove Busund, MD, PhD‡¶*

(*J Thorac Oncol.* 2011;6: 824–833)

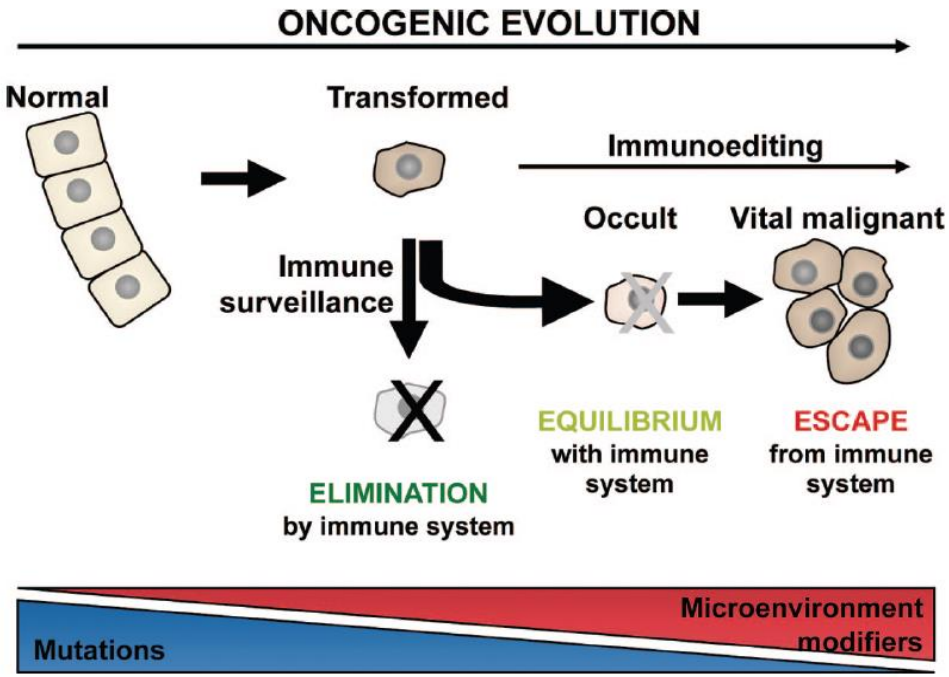

FIGURE 2. Integration of immunoediting and oncogenesis during cancer progression. Oncogenesis leads to transformed cells, which are attacked by immune cells due to neoantigen presentation. This immune surveillance imposes a selection for transformed cells that acquire tactics to escape control. Their genetic instability facilitates evolution of strategies for immune evasion or suppression, which may tilt the tumor microenvironment from hostile to supportive for the transformed cells. At one point, a state of equilibrium may be achieved, corresponding to a clinically occult dormant disease. Further iteration of evasion mechanisms may ultimately drive immune suppression beyond the local microenvironment, accomplishing immune escape and in this manner licensing invasive and metastatic behavior. Adapted from *Oncogene*.[30]

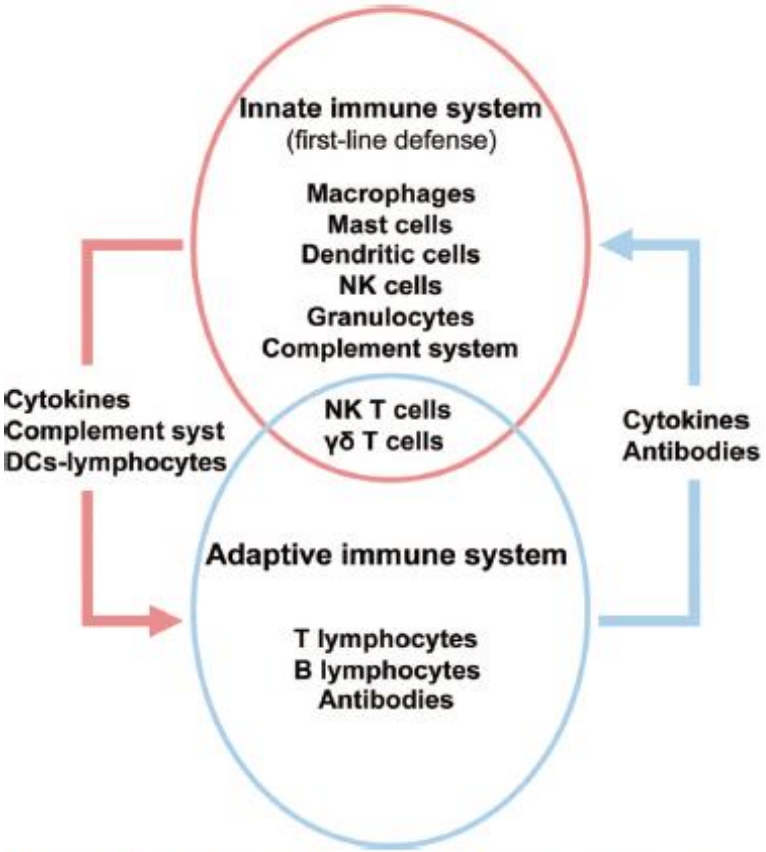

FIGURE 1. Schematic presentation of the interplay between innate and adaptive immunity. NK T cells and $\gamma\delta$ T cells play their roles in the crossroad between the innate and adaptive immune system. The crosstalk between these immune systems is mediated by complex interactions between cells of both immune subsets and their soluble factors. The innate immune system, i.e., the first line of immune defense, regulates adaptive immune responses by the production of cytokines, interactions between dendritic cells and lymphocytes, and activation of the complement system. The adaptive immune system modulates innate immune responses by cytokine and antibody production. Adapted from *Cancer Immunol Immunother.*[9] DCs, dendritic cells; NK, natural killer; NT T cells, natural killer T cells.

TABLE 1. Markers and Functions of Immune Cells in the Tumor Microenvironment

Cell Type	Functions in the Tumor Microenvironment	References
TAM	Classically activated macrophages (M1) contribute to tumor rejection, whereas alternatively activated macrophages (M2) promote angiogenesis and tissue remodeling. TAMs, sharing M2 characteristics, are tumor promoting and associated with poor prognosis.	55–57, 64–66
MDSC	Increased in almost all patients with cancer. Suppressive effect with respect to T cells.	28, 57, 58
MSC	Infiltrate different human cancers. In animal models, they increase cancer cell dissemination. Also found to be immunosuppressive, in part through inhibition of T-cell proliferation.	71–74
Mast cell	Important for generating and maintaining innate and adaptive immune responses. Increased numbers of mast cells correlate in some cases with poor prognosis. Have been implicated in angiogenic switch in animal models.	57, 60
TEM	Implicated in angiogenesis in animal models. Have been detected in human tumors and at low frequency in the peripheral blood of cancer patients.	57, 61, 62
Neutrophil	Neutrophil levels are increased in patients with colon, gastric, and lung cancer. Increased neutrophil numbers are associated with poor prognosis in bronchioalveolar carcinoma. Neutrophils have been associated with angiogenesis and metastasis in animal models.	57, 87
NK cell	Effector lymphocytes of the innate immune system. Are cytotoxic to cancer cells. Important role in immunosurveillance of cancer.	13, 80, 81
NK T Cell	T cells cytotoxic to cancer cells and contribute to immunosurveillance of cancer. Type 2 NK T cells have been reported to down-regulate tumor immunosurveillance and suppress antitumor responses.	29, 84, 85
T helper cells	$CD4^+$ T helper cells aid $CD8^+$ T cells in tumor rejection.	2, 28, 87
Cytotoxic T cells	CTLs are effector cells of adaptive immunity and specifically recognize and destroy cancer cells.	2, 87, 90
Regulatory T cells	Treg cells are $CD4^+$ lymphocytes, characterized by presenting the phenotype CD25+CD127-Foxp3+. Treg cells are a subset of T cells with the ability to suppress harmful immunological reactions to self- and foreign antigens and have also been attributed to polarize immunity away from an antitumor response, block $CD8^+$ T cell activation and NK cell killing.	2, 28, 86, 88, 90, 106
B cell	B lymphocytes are essential mediators of the adaptive immune system, but in an animal model of squamous cell carcinoma, it was demonstrated to promote malignancy.	44, 87

CTL, $CD8^+$ cytotoxic T cells; MDSC, myeloid-derived suppressor cells; MSC, mesenchymal stem cells; NK cells, natural killer cells; NK T cells, natural killer T lymphocytes; TAM, tumor-associated macrophage; TEM, TIE2-expressing monocyte; TIE2, angiopoietin receptor; Treg cells, regulatory T cells.

Clinical Cancer Research

Review

Prognostic Immune Markers in Non–Small Cell Lung Cancer

Kei Suzuki[1], Stefan S. Kachala[1], Kyuichi Kadota[1,5], Ronglai Shen[2], Qianxing Mo[2], David G. Beer[6], Valerie W. Rusch[1], William D. Travis[3], and Prasad S. Adusumilli[1,4]

Abstract

Tumor-associated immune responses have polarized effects in regulating tumor growth. Although a clear association has been shown between the tumor immune response and clinical outcome in colorectal and ovarian cancers, the role of immune markers for stratifying prognosis in non–small cell lung cancer (NSCLC) is less defined. Herein, we review the prognostic significance of published immune markers in the tumor microenvironment and peripheral blood of NSCLC patients. To identify prognostic immune genes, we reviewed all published gene-profiling studies in NSCLC and delineated the significance of immune genes by doing subanalysis on the microarray database of the NIH Director's Challenge study. This first comprehensive review of prognostic immune markers provides a foundation for further investigating immune responses in NSCLC. *Clin Cancer Res; 17(16); 5247–56. ©2011 AACR.*

Role	Author	No. points	Stages	Observation and/or conclusion	Survival advantage
TIL	Johnson et al. (7)	95	I, 54 (57%)		
			II, 17 (18%)	High CD3+ and S100+ in tumor correlated with longer OS	
			III, 20 (21%)		
	Hiraoka et al. (9)	109	I, 67 (61%)	Concurrent high CD4+ and CD8+ in stroma correlated with longer survival	
			II–III, 42 (39%)		
	Kikuchi et al. (10)	161	I, 95 (59%)	HLA class I expression correlates with longer OS in stage I	
			II–IV, 66 (41%)	HLA class I expression correlated with CD8+ cells	
	Ruffini et al. (15)	1,290	I, 714 (55%)		
			II, 265 (21%)	TIL (mostly CD8+) in tumor correlated with better OS	
			IIIA, 214 (17%)		
	Wakabayashi et al. (16)	178	I, 107 (60%)	High CD4+ in stroma correlated with longer OS	5-year OS 64% versus 43%
			II, 23 (13%)	High CD8+ in tumor correlated with shorter OS	5-year OS 47% versus 60%
			IIIA, 48 (27%)		
	Al-Shibli et al. (17)	335	I, 212 (63%)	High CD4+ in stroma correlated with longer DSS	5-year DSS 63% versus 42%
			II, 91 (27%)	High CD8+ in stroma correlated with longer DSS	5-year DSS 75% versus 53%
			IIIA, 32 (10%)	High CD20+ in stroma correlated with longer DSS	5-year DSS 61% versus 32%
	Pelletier et al. (18)	113	I, 66 (58%)		
			II, 20 (18%)	Peritumoral CD20+ correlated with longer survival	
			III, 29 (26%)		

Ti-BALT	Dieu-Nosjean et al. (19)	74	I, 62 (84%) IIA, 12 (16%)	High mature DCs in tertiary lymphoid structures correlated with longer survival	4-year DFS 88% versus 51%
Treg	Shimizu et al. (20)	100	I, 68 (68%)	High FoxP3+ correlated with shorter time to recurrence	
			II, 14 (14%)	COX-2 expression correlated with shorter time to recurrence	
			III, 18 (18%)	COX-2 expression correlated with FoxP3+ infiltration	
	Petersen et al. (23)	64	I, 64	High proportion of FoxP3+ among TIL in tumor correlated with shorter DFS	Median DSS of 53 months, 63 months, and >72 months for high, intermediate, and low risk group
TAM	Chen et al. (25)	35	I, 14 (40%)	TAM in stroma correlated with shorter OS	
			II, 4 (11%)	TAM-tumor interaction upregulated IL-8 mRNA expression	Median OS 16 months versus 45 months
			III, 17 (49%)		

Role	Author	No. points	Stages	Observation and/or conclusion	Survival advantage
	Zeni et al. (26)	47	I, 24 (51%)	IL-10 high TAMs associated with shorter OS	
			II–IV, 23 (49%)	IL-10 high TAMs associated with advanced stage	
	Ho et al. (27)	68	I, 24 (35%)		
			II, 15 (22%)	Increased high TREM-1 macrophages correlated with shorter DFS and OS	Median DFS 22 months versus not reached
			III, 29 (43%)		Median OS 29 months versus not reached
	Kim et al. (28)	144	I, 79 (55%)		
			II, 25 (17%)	TAM in tumor correlated with longer OS	5-year OS 64% versus 39%
			III, 38 (26%)		
	Welsh et al. (29)	175	I, 79 (45%)		
			II, 44 (25%)	High TAM in tumor correlated with longer OS	5-year OS of 53% versus 8%
			IIIA, 34 (19%)		
	Ohri et al. (32)	40	I, 26 (65%)		
			II, 8 (20%)	Increased M1 in long survivors	
			III, 6 (15%)		
	Ohtaki et al. (33)	170	IA, 95 (56%)	High stromal CD204+ (M2) associated with shorter survival	5-year OS of 61% versus 89%
			IB–IIIA, 75 (44%)		

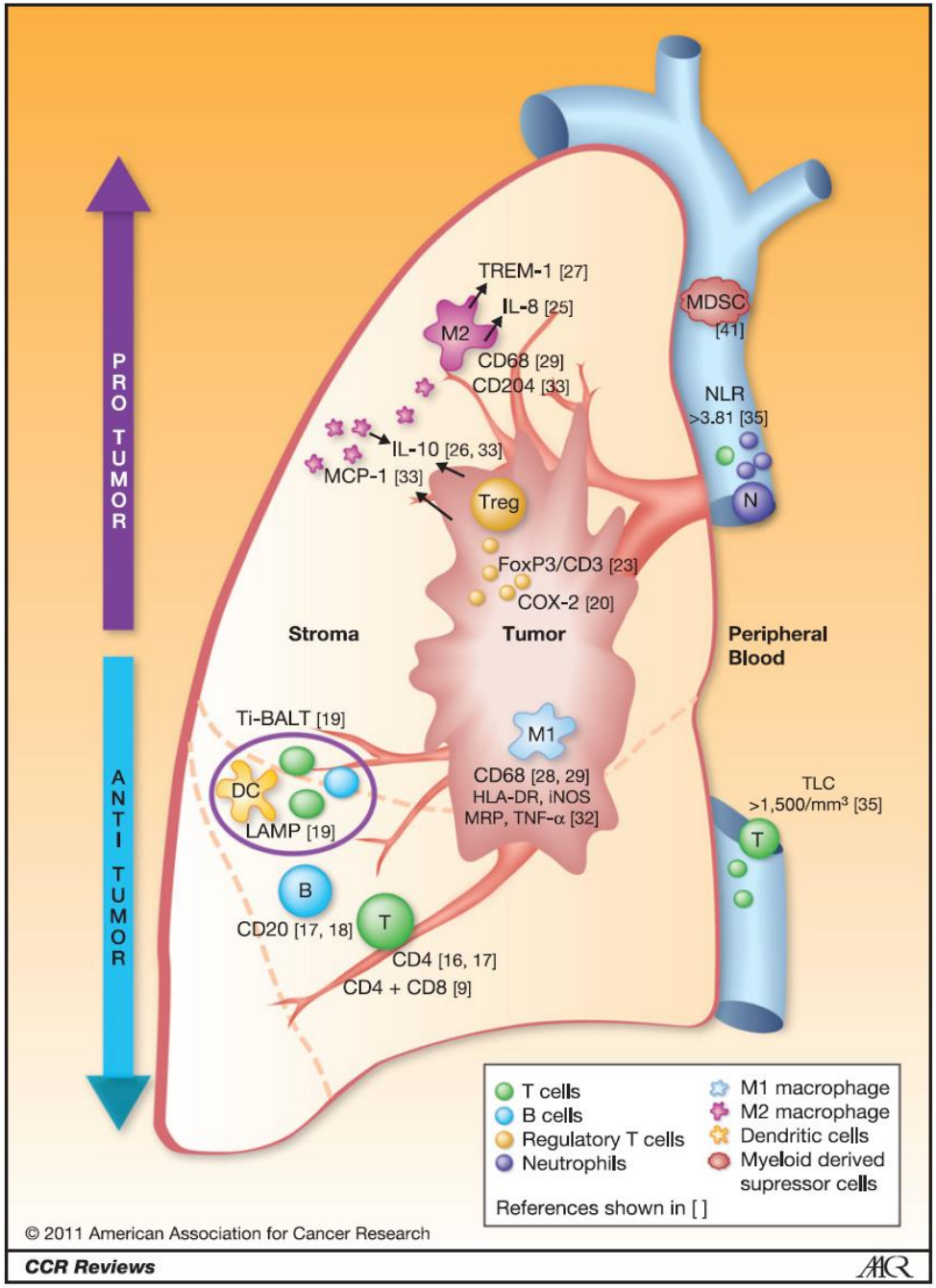

Figure 1. Prognostic immune markers in NSCLC. T cells and B cells are associated with longer survival when found in the stroma along with Ti-BALT, which contains Lamp+ DCs. In contrast, FoxP3+ Tregs in the tumor are associated with shorter survival. Antitumor M1 macrophages are characterized by HLA-DR, iNOS, MRP, and TNF-α. Protumor M2 macrophages express CD204. M2 expression of IL-8, IL-10, and TREM-1 (delineated by arrows) has been shown to correlate with shorter survival. Tumoral expression of COX-2 recruits FoxP3+ Treg cells, whereas expression of IL-10 and MCP-1 recruits M2 macrophages. In the peripheral blood, immune suppression is associated with poor clinical outcomes revealed by low total lymphocyte counts (TLC) and elevated NLRs.

Réponse immunitaire dans les cancers bronchopulmonaires

A.-P. Meert[1, 2], T. Berghmans[1], C. Mascaux[1], J.-P. Sculier[1]

Résumé

Introduction La réponse immunitaire antitumorale est essentiellement de type cellulaire et de nombreuses recherches sont conduites afin d'augmenter celle-ci, à visée thérapeutique.

Etat des connaissances Une activation du système immunitaire a été rapportée dans des stades précoces de cancer bronchique. Par contre, de nombreuses études ont montré un certain degré d'immunosuppression chez les patients porteurs d'une maladie cancéreuse avancée préalablement à tout traitement immunosuppresseur et, plus particulièrement, une altération de leur immunité cellulaire. La présence d'un infiltrat leucocytaire est un indicateur d'une réponse active de l'hôte contre la tumeur. Plusieurs syndromes paranéoplasiques, liés à la présence d'auto-anticorps, ont été décrits, plus particulièrement en cas de cancer bronchique à petites cellules. D'autres anticorps, non associés à des syndromes paranéoplasiques, ont également été mis en évidence, principalement dirigés contre le gène suppresseur de tumeur p53. L'immunothérapie active non spécifique (bacille de Calmette Guérin, interférons, interleukines...), l'immunothérapie passive (anticorps monoclonaux) et l'immunothérapie adoptive sont étudiées depuis de nombreuses années avec des résultats peu satisfaisants. L'immunothérapie active spécifique (vaccination antitumorale et thérapie génique) est à l'heure actuelle la voie la plus étudiée.

Perspectives Le ciblage correct des patients susceptibles de bénéficier de traitements immunomodulateurs, la spécificité et l'efficacité des vecteurs, l'expression des gènes d'intérêt et le risque d'infection et de dissémination lors des essais cliniques sont des problèmes en cours d'investigation.

Conclusion Des manipulations de la réponse immunitaire ont été et sont réalisées afin d'en améliorer l'efficacité. La vaccination anti-tumorale et la thérapie génique sont les voies les plus étudiées.

Mots-clés : Cancer Bronchopulmonaire • Immunité • Immunothérapie • Vaccination • Anticorps.

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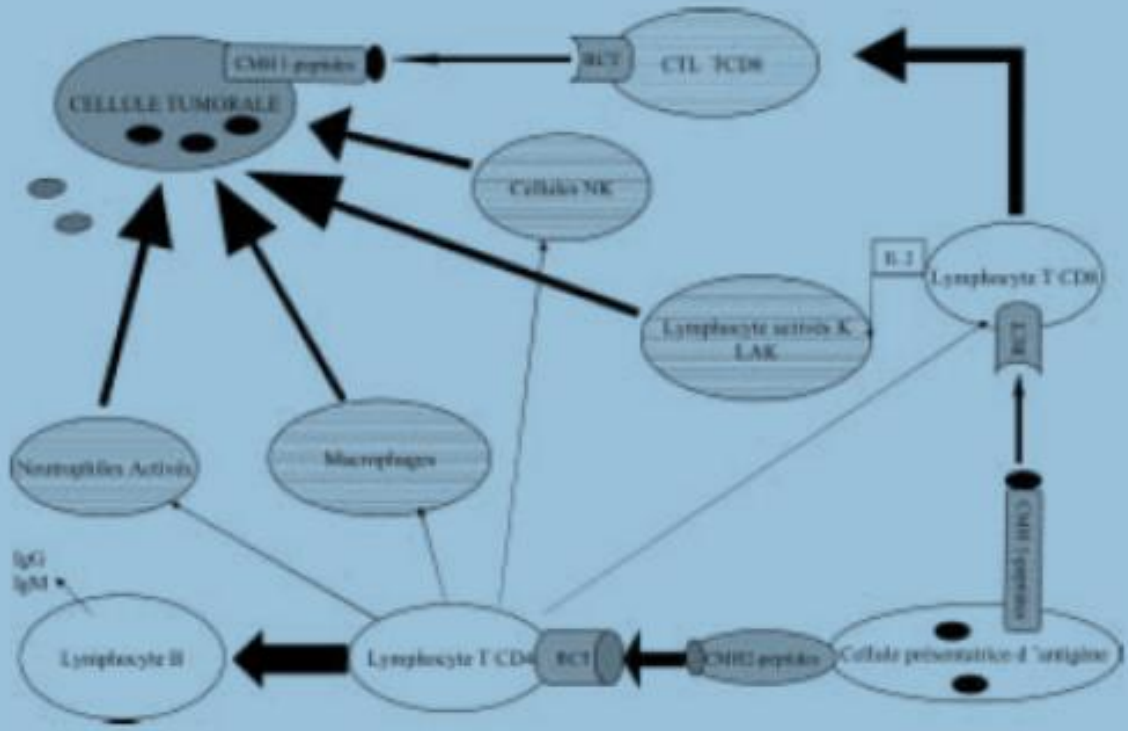

Fig. 1.
Schéma général de l'immunité antitumorale. Les lymphocytes T CD8 sont activés par la liaison de leur récepteur (RTC) avec le complexe molécule d'histocompatibilité (CMH) de classe 1 en association avec les peptides endogènes (par exemple tumoraux), préalablement endocytés par les cellules présentatrices d'antigène. Les lymphocytes T CD4 sont activés par la liaison de leur RTC avec le CMH de classe 2 en association avec les peptides exogènes et sécrètent ensuite des cytokines qui activent non seulement les lymphocytes B, mais également des cellules à potentiel cytolytique antitumoral (les macrophages, les lymphocytes T CD8 (CTL), les neutrophiles activés et les cellules « natural killer » (NK)). Un cinquième type d'acteur de la lyse tumorale, les lymphocytes activés « killer » ou LAK, sont activés par la sécrétion d'IL2 par les lymphocytes T CD8.

CCR New Strategies

Clinical Cancer Research

New Strategies in Lung Cancer: Translating Immunotherapy into Clinical Practice

Patrick M. Forde, Ronan J. Kelly, and Julie R. Brahmer

Abstract

Recent breakthroughs in translating the early development of immunomodulatory antibodies into the clinic, notably with the anti–cytotoxic T-lymphocyte antigen-4 antibody, ipilimumab, have led to durable benefits and prolonged survival for a subgroup of patients with advanced melanoma. Subsequent studies have shown that related immune checkpoint antibodies, specifically those targeting the programmed death-1 pathway, have activity in non–small cell lung cancer. Non–small cell lung cancer is the commonest cause of cancer death worldwide and this exciting avenue of clinical investigation carries with it great promise and new challenges. In this article, we discuss recent developments in lung cancer immunotherapy, reviewing recent findings from therapeutic vaccine studies and in particular we focus on the refinement of immunomodulation as a therapeutic strategy in this challenging disease. *Clin Cancer Res; 20(5); 1067–73. ©2014 AACR.*

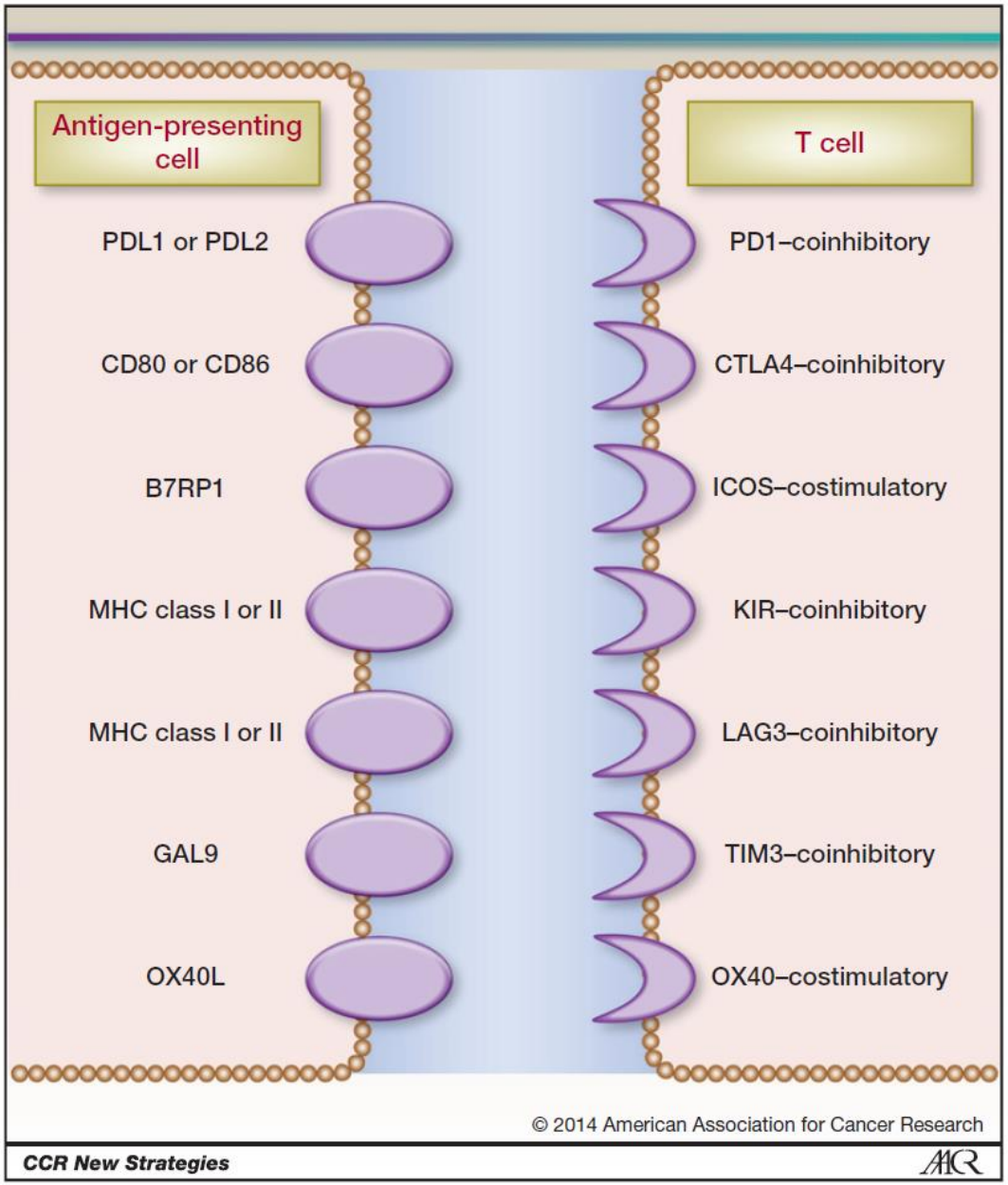

Figure 1. Selected immune checkpoints for which modulating molecules are in late preclinical or clinical development. B7RP1, B7-related protein-1; ICOS, inducible T-cell costimulator; KIR, killer cell immunoglobulin–like receptor; LAG3, lymphocyte-activation gene 3; GAL9, galectin-9; TIM3, T-cell immunoglobulin domain and mucin domain 3; OX40L, OX40 ligand.