Renal Safety and Angiotensin II Blockade Medications in Patients Undergoing Non-Emergent Coronary Angiography: A Randomized Controlled Study

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ABSTRACT: **Background:** Contrast-induced nephropathy (CIN) is one of the major causes of new-onset renal failure in hospitalized patients. Although renin-angiotensin-aldosterone system (RAAS) blocking agents are widely used among patients requiring contrast studies, data on the effect of these agents on the development of CIN are sparse and inconsistent.

Objectives: To evaluate in a randomized controlled trial whether uninterrupted administration of angiotensin II (AngII) blockade medications influence estimated glomerular filtration rate (eGFR) in patients undergoing non-emergent coronary angiography.

Methods: Patients receiving treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARB) were recruited consecutively. The enrolled subjects were randomized into three groups at a 1:1:1 ratio: group A (ACE/ARB stopped 24 hours prior to the procedure and restarted immediately after the procedure), group B (ACE/ARB stopped 24 hours prior to the procedure and restarted 24 hours after the procedure), and group C (ACE/ARB continued throughout the study period). Plasma creatinine was measured and eGFR was calculated according to the Cockroft-Gault equation before and 48 hours after the coronary angiography. The primary endpoint was a change in eGFR at 48 hours.

Results: Groups A, B and C comprised 30, 31 and 33 patients respectively. The mean age of the study population was 65 ± 12 years and 67% were males. Fifty percent of the subjects had diabetes mellitus. The primary endpoint analysis showed that at 48 hours after the procedure there was no difference in ΔeGFR between groups A and C (4.25 ± 12.19 vs. 4.65 ± 11.76, $P = 0.90$) and groups B and C (3.72 ± 17.42 vs. 4.65 ± 11.76, $P = 0.82$). In post-hoc analysis the patients were clustered according to the following groups: medical alternation (group A and B) versus control (group C), and to baseline eGFR ≥ 60 ml/min vs. eGFR < 60 ml/min. In patients with baseline eGFR < 60 ml/min the ΔeGFR (baseline eGFR-eGFR 48 hours post-angiography) was significantly different between the intervention vs. control group (median 5.61 vs. median -2.19, $P = 0.03$ respectively). While in patients with baseline eGFR ≥ 60 ml/min there was no significant difference in ΔeGFR between the intervention and control groups.

Conclusions: ACE-I and ARB can safely be used before and after coronary angiography in patients with eGFR ≥ 60 ml/min.

IMAJ 2013; 15: 682–687

KEY WORDS: angiotensin II (AngII), contrast-induced nephropathy (CIN), estimated glomerular filtration rate (eGFR), non-emergent coronary angiography

Contrast-induced nephropathy is defined as an absolute or relative increase in serum creatinine compared to the baseline values, together with exposure to a contrast agent and exclusion of alternative explanations for renal impairment. Most frequently the renal impairment develops 48 hours post-exposure [1]. CIN is one of the major causes of new-onset renal failure in hospitalized patients [2]. The reported Israeli experience found low CIN in general hospitalized patients (4.6%) and high rates (44%) in selected high risk subgroups of patients (with renal insufficiency or diabetes mellitus). Furthermore, prolonged length of stay and high in-hospital mortality were directly related to CIN severity [3]. The reported CIN rate after coronary catheterization ranges between 2% and 25% [4,5]. The prognosis of patients with CIN who require dialysis is grave, with mortality approaching 40% and 2 year survival of less than 20% [6,7].

Although angiotensin II blocking agents are widely used in patients requiring contrast studies, data on the effect of these agents on the development of CIN are sparse and inconsistent. While some reports showed that the AngII

CIN = contrast-induced nephropathy
ANG11 = angiotensin II

blocking agents were accountable for the increased risk of CIN [8,9], others demonstrated that angiotensin-converting enzyme inhibitors were either protective of kidney from CIN development [10,11] or had no effect [12]. Patients undergoing percutaneous coronary intervention are frequently treated with renin-angiotensin-aldosterone system blocking agents. Despite the frequent utilization of AngII blockade in patients undergoing percutaneous coronary angiography, no guidelines are available on the topic of the cessation of either ACE-I or ARB prior to the procedure.

The aim of the current study was to evaluate prospectively whether concomitant administration of AngII blockers (namely ACE-I and ARB) influences the change in estimated glomerular filtration rate after administration of contrast media in patients undergoing non-emergent coronary angiography.

PATIENTS AND METHODS

After providing informed consent the consecutive patients scheduled for non-emergent coronary angiography in internal medicine departments of Soroka University Medical Center between 1 April and 30 September 2010 were enrolled in the study. Inclusion criteria were age > 18 years, chronic therapy of at least one month with ACE-I and/or ARB (confirmed by electronic records in their medical file), and scheduled coronary angiography. Exclusion criteria were chronic use of non-steroidal anti-inflammatory and cyclo-oxygenase-2 selective inhibitors, chronic treatment with mineralocorticosteroid receptor blocker, chronic treatment with renin antagonist, systolic blood pressure < 90 mmHg, and administration of contrast within 14 days of enrollment. The enrolled subjects were randomized into three groups at a 1:1:1 ratio in groups of six:

THE MEDICAL ALTERNATION GROUPS

- Group A: ACE/ARB stopped 24 hours prior to the procedure and restarted immediately after
- Group B: ACE/ARB stopped 24 hours prior to the procedure and restarted 24 hours after

THE CONTROL GROUP

- Group C: ACE/ARB continued throughout the study period

Primary analysis compared the change in eGFR (ΔeGFR) from baseline to 48 hours after exposure to the contrast. Secondary endpoints included creatinine decrease of > 25% from baseline and the requirement of unscheduled therapy for elevated blood pressure.

ACE-1 = angiotensin-converting enzyme inhibitors
ARB = angiotensin receptor blockers

SUBGROUP ANALYSIS

The study population was grouped according to medical alternation (group A and B) versus control (group C) and according to baseline eGFR ≥ 60 ml/min vs. eGFR < 60 ml/min. The influence of AngII blockade on diabetes mellitus (present vs. absent) and GFR ≥ 60 ml/min vs. GFR < 60 ml/min was tested in two groups: the medical alternation group (group A and B) compared to the control group (group C). An additional analysis was performed to adjust for age and left ventricular function.

STUDY PROTOCOL

The eligible patients were enrolled at least 24 hours prior to the planned procedure. The patients followed the standard protocol for the preparation for PCI inclusive of full saline administration 12 hours before and 12 hours after the image study together with 600 mg twice daily of N-acetylcysteine 24 hours before and 24 hours after the image study as recommended [13,14]. Our study was performed before the results of the Acetylcysteine for Contrast-Induced Nephropathy Trial were published [15]. The standard practice in our institute was not to stop ACE/ARB before or after the procedure (Group C, reference group). Since most of the patients had a baseline eGFR > 60 ml/min, eGFR was calculated according to the Cockroft-Gault equation.

PATIENT DATA

Patient data were recorded according to standard protocol and included demographic and clinical data, a regular medical regimen, and averaged daily blood pressure. For each subject the following measurements were obtained during the hospitalization: total cholesterol, low density lipoprotein, high density lipoprotein, triglyceride and HbA1c levels. The study was approved by the institutional ethics committee.

EFFECT ESTIMATION

Due to the limited resources we planned to enroll 100 subjects. Therefore, we calculated the difference between the groups we were able to exclude. The comparisons of interest in this study were between groups A (ACE/ARB stopped 24 hours prior to the procedure and restarted immediately after) vs. B (ACE/ARB stopped 24 hours prior to the procedure and restarted 24 hours after), and C (ACE/ARB continued throughout the hospitalization) vs. B, with a significance level for each at $\alpha = 0.05$ (two-sided). Due to the exploratory nature of this study, no adjustments for multiple comparisons were made. We used the following assumptions for the difference that we were able to exclude:

- Each medical alternation group (A or B) tested separately versus reference group (C)

PCI = percutaneous coronary angiography

Table 1. Clinical characteristics of the study population (mean ± SD)

		Group A (n=30)	Group B (N=31)	Group C (n=33)	*P* value
Age (yr)		64.81 ± 13.82	61.03 ± 11.29	67.64 ± 9.02	0.08
Height (cm)		168.90 ± 7.66	169.27 ± 9.60	166.06 ± 9.62	0.30
Weight (kg)		82.80 ± 13.98	82.92 ± 15.06	81.44 ± 14.71	0.90
Gender	Male n(%)	23 (74.2)	21 (70.0)	18 (56.3)	0.29
Indication for catheterization n(%)	NSTEMI	6 (20.0)	7 (24.1)	8 (25.0)	0.31
	STEMI	1 (3.3)	0 (0.0)	0 (0.0)	
	Unstable angina	20 (66.7)	16 (55.2)	22 (68.8)	
	Stable angina	0 (0.0)	0 (0.0)	1 (3.1)	
	Positive stress test	1 (3.3)	5 (17.2)	1 (3.1)	
	Other	2 (6.7)	1 (3.4)	0 (0.0)	
Background diseases and risk factors n(%)	CIHD	23 (74.2)	19 (63.3)	21 (63.6)	0.58
	HTN	29 (93.5)	27 (90.0)	33 (100.0)	0.20
	Diabetes mellitus	16 (51.6)	14 (46.7)	17 (51.5)	0.93
	Non-insulin requiring	10 (33.3)	9 (29.0)	13 (39.4)	
	HbA_1C (%)	7.14 ± 2.32	7.17 ± 2.26	6.76 ± 1.13	0.66
	Insulin requiring	6 (20.0)	5 (16.7)	4 (12.1)	0.69
	LDL (mg/dl)	79.00 ± 30.13	86.96 ± 31.93	91.07 ± 33.98	0.35
	HDL (mg/dl)	41.30 ± 17.32	38.07 ± 13.20	44.66 ± 10.87	0.19
LV function n(%)	Normal	14 (46.7)	17 (58.6)	21 (72.4)	0.07
	Mild	5 (16.7)	7 (24.1)	4 (13.8)	
	Moderate	7 (23.3)	3 (10.3)	4 (13.8)	
	Severe	4 (13.3)	2 (6.9)	0 (0.0)	
Smoker n(%)	Current	8 (25.8)	7 (24.1)	4 (12.1)	0.05
	Former	12 (38.7)	8 (27.6)	5 (15.2)	
Medications n(%)	Aspirin	29 (93.5)	27 (90.0)	32 (97.0)	0.53
	Statins	30 (100.0)	28 (93.9)	31 (93.9)	0.37
	Beta-blocker	27 (87.1)	23 (79.3)	26 (83.8)	0.11
	Diuretics	10 (35.7)	7 (24.1)	7 (21.9)	0.41
	Ca channel blocker	7 (24.1)	8 (28.6)	12 (37.5)	0.51
	ACE inhibitors	22 (70.0)	25 (80.0)	26 (74.2)	0.67
	AngII receptor antagonists	8 (27.6)	6 (21.4)	7 (24.1)	0.86
Volume of contrast media (ml)		119.0 ± 68.2	105. 7 ± 56.7	115.5 ± 61.3	0.69
Coronary anatomy n(%)	No. of lesions	1.8 ± 1.2	1.5 ± 0.9	1. 5 ± 1.2	0.50
	No. of vessels	1.6 ± 1.3	1.43 ± 0.93	1.48 ± 1.2	0.82
PCI	No. of patients with PCI	11 (35.5)	10 (33.3)	15 (45.5)	0.57
	No. of stents/ patient	1.18 ± 0.41	1 ± 0	1.13 ± 0.52	0.34

NSTEMI = non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction, CIHD = chronic ischemic heart disease, HTN = hypertension, LDL = low density lipoprotein, HDL = high density lipoprotein, PCI = percutaneous coronary angiography

- Type I error (α) = 0.05 (two-sided)
- Statistical power (1-β) = 80% Sample size 33 subjects per group.

Thirty-three subjects per group were enrolled to show that a difference in eGFR change at 48 hours between either group A and group C or group B and group C will be higher than 10 ± 15 ml/min. The sample size includes an estimated 10% combined loss to follow-up.

STATISTICAL ANALYSIS

The results are presented as the mean (SD) for continuous variables and as the total number of patients (percentage of total patients) for categorical data. ANOVA was used for comparison of the continuous variables or chi-square test for categorical data. We used the Mann-Whitney test for the comparison of variables with a not normal distribution (presented as median and interquartile range). A repeated measures analysis adjusted for the baseline levels was performed to compare creatinine, urea and eGFR measures before and 24 and 48 hours after the catheterization between the three groups. A two-tailed *P* value of ≤ 0.05 was considered significant. The statistical analysis was done using SPSS version 17.

RESULTS

Between April and September 2010 we recruited 99 patients into the study. Five patients did not undergo coronary catheterization and were therefore excluded from the analysis; 94 patients completed the study protocol. There were 30 patients in group A (ACE/ARB stopped 24 hours prior to the procedure and restarted immediately after), 31 in group B (ACE/ARB stopped 24 hours prior to the procedure and restarted 24 hours after), and 33 in group C (ACE/ARB continued throughout the hospitalization).

CLINICAL CHARACTERISTICS [TABLE 1]

The mean age of the study population was 65 ± 12 years and 67% were males. There was no difference in age between group A, B and C (*P* = 0.08). The gender distribution was also comparable between the groups: 74%, 70% and 56% males respectively (*P* = 0.29). Overall, the most common indication for coronary catheterization was unstable angina (62%) with no differences between the groups (*P* = 0.31). Diabetes mellitus was found in 50% of the subjects.

The medical treatment the subjects received prior to the procedure was comparable between the groups, with a high prevalence of statins (96%), aspirin (94%), and beta-blockers (86%). All patients were pretreated with clopidogrel. The amount of contrast media the subjects received during catheterization did not differ between the groups (119.0 ± 68.2, 105.7 ± 56.7 and 115.5 ± 61 ml respectively, *P* = 0.69).

Percutaneous coronary intervention was performed in 36%, 33% and 46% in groups A, B and C respectively ($P = 0.57$). The number of treated lesions, vessels and stents was similar between the groups.

BLOOD PRESSURE

The blood pressure measurements did not differ significantly between the three study groups at recruitment (systolic/diastolic blood pressure 124.8 ± 15.7/69.3 ± 13.2, 126.7 ± 16.4/75.1 ± 9.8 and 132.8 ± 14.0/73.8 ± 11.8 respectively, $P = 0.12/0.11$). ANOVA repeated measures test adjusted for the baseline levels revealed no difference between the groups over the study period (systolic/diastolic blood pressure 127.3 ± 14.3/69.8 ± 11.9, 129.9 ± 15.8/71.2 ± 8.7 and 127.8 ± 27.4/71.5 ± 12.7 respectively, $P = 0.88/0.82$). All three groups demonstrated lower blood pressure during hospitalization as compared to measurements at admission. Temporary cessation of ACE-I or ARB was not followed by a significant increase in blood pressure, and only two patients needed an additional antihypertensive treatment, both of which were in group A (ACE/ARB stopped 24 hours prior to the procedure and restarted immediately after).

RENAL FUNCTION [TABLE 2]

Baseline creatinine value was comparable between the three groups (1.01 ± 0.40, 0.94 ± 0.38 and 0.92 ± 0.21 respectively, $P = 0.6$). The primary endpoint analysis showed that at 48 hours after the procedure there was no difference in ΔeGFR between groups A and C (3.58 ± 10.37 vs. 4.68 ± 11.04, $P = 1.00$) and groups B and C (1.03 ± 16.95 vs. 4.68 ± 11.04, $P = 0.95$). Although no change in ΔeGFR was demonstrated between the groups, there was an increase in eGFR in the control group 48 hours after angiography. While in group B (AngII blockade stopped 24 hours before and after angiography) there was a decrease, there was a decrease in eGFR 48 hours after angiography. Overall six patients (6.4%) had a creatinine increase of 25% above the baseline level: five in groups A and B and one in group C.

PCI AND RENAL FUNCTION

Sensitivity analysis was performed for percutaneous coronary intervention. Fifty-seven patients underwent diagnostic catheterization versus 38 patients who underwent PCI. There was no significant difference in any eGFR measurement including ΔeGFR (before versus 48 hours post-catheterization) between the different study groups (A, B and C) in both the diagnostic catheterization and the PCI group: 2.74 ± 11.72, 1.57 ± 19.36, 3.70 ± 13.75, $P = 0.57$; and 5.16 ± 7.43, 6.25 ± 9.66, 5.91 ± 6.65, $P = 0.95$ respectively. A comparison between the total number of patients who underwent only diagnostic catheterization versus patients who underwent PCI also did not show a significant influence on the ΔeGFR (1.64 ± 14.98 vs. 5.15 ± 7.75 respectively, $P = 0.22$).

Table 2. Renal function measurements (mean ± SD)

		Group A (n=30)	Group B (N=31)	Group C (n=33)	*P* value
Before catheterization	Creatinine (mg/dl)	1.01 ± 0.40	0.94 ± 0.38	0.92 ± 0.21	0.60
	Urea (mg/dl)	49.65 ± 19.73	42.40 ± 17.07	42.15 ± 23.05	0.26
	GFR* (ml/min)	84.23 ± 30.53	91.38 ± 29.09	84.34 ± 22.40	0.51
24 post-catheterization	Creatinine (mg/dl)	0.92 ± 0.30	0.87 ± 0.23	0.82 ± 0.25	0.30
	Urea (mg/dl)	32.97 ± 12.27	31.83 ± 12.70	34.00 ± 17.26	0.84
	GFR (ml/min)	90.12 ± 27.12	96.09 ± 26.43	92.99 ± 22.80	0.66
48 hours post-catheterization	Creatinine (mg/dl)	0.99 ± 0.34	0.95 ± 0.28	0.88 ± 0.27	0.34
	Urea (mg/dl)	38.69 ± 13.13	38.96 ± 14.20	39.71 ± 16.52	0.96
	GFR (ml/min)	85.34 ± 28.85	88.34 ± 28.07	89.44 ± 25.78	0.85
Δ Before minus 48 hours post-catheterization	ΔCreatinine (mg/dl)	-0.03 ± 0.22	-0.06 ± 0.30	-0.04 ± 0.17	0.84
	ΔUrea (mg/dl)	11.69 ± 15.89	-5.83 ± 12.58	1.25 ± 11.93	0.01#
	ΔGFR (ml/min)	3.58 ± 10.37	1.03 ± 16.95	4.68 ± 11.04	0.59
48 hours post-catheterization/ before catheterization (*100)	Creatinine (mg/dl)	110.43 ± 14.98	116.76 ± 98.84	95.41 ± 17.60	0.49
	GFR (ml/min)	106.43 ± 4.98	103.94 ± 19.24	105.49 ± 14.45	0.86

POST-HOC ANALYSIS: ANGII BLOCKADE IN PATIENTS WITH BASELINE EGFR < 60 ML/MIN AND DIABETES

The study population was clustered in two groups: both medical alternation groups (group A and B) compared to the control group (group C).

In patients with baseline eGFR ≥ 60 ml/min the intervention did not change the eGFR (there was a slight decrease of eGFR in the intervention group, $P = 0.32$). However, in patients with eGFR < 60 ml/min there was a significant difference in eGFR change between medical alternation and control. Cessation of AngII blockade (both medical alternation groups) resulted in significant elevation of eGFR 48 hours after coronary angiography, while in the control group there was a decrease in eGFR (median 5.61 interquartile (0.72–11.20 vs. mean -2.19 IQ 12.94–2.38, $P = 0.03$ respectively) [Table 3]. The presence or absence of diabetes mellitus did not change significantly the difference in ΔeGFR between the intervention and the control group [mean 4.08 IQ (-2.83–9.75) vs. mean 2.54 IQ (0.00–7.21), $P = 0.87$; and mean 3.15 IQ (0.00–7.75) vs. mean 0.37 IQ (-2.60–12.93), $P = 0.81$ respectively]. Neither age nor left ventricular function had a significant effect on the difference in ΔeGFR between the treatment groups. Post-hoc sensitivity analysis with adjustment for age in covariant linear multivariant regression model revealed that the treatment group *w*ith adjustment for age ($P = 0.86$) was not associated with difference in GFR change ($P = 0.45$ for treatment). The treatment group with adjustment of left

IQ = interquartile

Table 3. Influence of RAAS blockade on eGFR after coronary angiography in patients with eGFR ≥ 60 ml/min vs. patients with eGFR < 60 ml/min

	Baseline eGFR ≥ 60 ml/min (N=72)			Baseline eGFR < 60 ml/min (N=21)		
	Medical alternation*	Control#	*P* value	Medical alternation*	Control#	*P* value
Baseline eGFR (ml/min)	110.25 (82.14–120.00)	88.35 (83.59–107.89)	0.02	51.79 (43.19–54.85)	53.92 (46.50–55.97)	0.25
eGFR after 48 hr (ml/min)	106.94 (80.29–120.00)	96.41 (82.63–118.11)	0.33	56.32 (47.64–64.09	46.38 (41.22–54.07)	0.16
Δ eGFR (ml/min) (after 48 hr baseline)	1.32 (0.00–7.46)	2.54 (0.00-12.69)	0.32	5.61 (0.72-11.20)	-2.19 (-12.94–2.38)	0.03
eGFR Baseline/48 hr*100	101.12 (100.0–109.1)	103.37 (100.0–114.5)	0.28	110.64 (101.8–121.9)	95.94 (76.95–105.95)	0.04

Median IQ range
*Group A & B
#Group C

ventricular function was not associated with difference in delta eGFR ($P = 0.21$).

DISCUSSION

The main finding in our study was that treatment with ACE-I or ARB in patients with eGFR ≥ 60 ml/min did not result in a significant change in eGFR after non-emergency coronary angiography. Post-hoc analysis showed that in patients with eGFR < 60 ml/min the use of AngII blockade before and after coronary angiography resulted in a significant decrease in eGFR after exposure to contrast media.

The role of the renin-angiotensin-aldosterone system blockade in the development of CIN is controversial. Some studies show no effect on renal outcome due to the RAAS blockade [12], while others demonstrate a renal hazard effect of RAAS blockade before exposure to contrast media [11].

In early experiments it was observed that the renin-angiotensin system plays a role in contrast-induced intrarenal vasoconstriction. The blockade of AngII decreased the duration of renal vasoconstriction following injection of contrast media [16]. The benefit of AngII blockade prior to contrast media exposure received further support from the clinical trial performed by Guta et al. [10] who showed that captopril administration in diabetic patients before exposure to contrast media reduced the incidence of CIN.

On the other hand, experimental observations indicated that AngII has a protective renal effect in CIN. These laboratory findings demonstrated that AngII induces the formation of transforming growth factor-beta 1, which protects the proximal tubule from contrast toxicity [17,18]. The harmful effect of AngII blockade in patients exposed to contrast media was demonstrated by several studies, most of them performed in patients with impaired renal function and in the elderly [9]. In the current study this concept was observed in the post-hoc analysis which demonstrated a significant reduction of eGFR in patients with baseline eGFR < 60 ml/min who continued AngII blockade throughout the study period.

RAAS = renin-angiotensin-aldosterone system

LIMITATIONS

Our study has several limitations. First, we were limited in our ability to enroll more patients, therefore we cannot exclude the possibility that a smaller difference between the groups might have been missed (type II error). Second, since the half-life of most ACE-I and ARB is more than 24 hours, AngII blockade should be discontinued at least 48 hours before the procedure.

CONCLUSIONS

Our main finding was that in patients with eGFR ≥ 60 ml/min it is safe and even protective to continue AngII blockade. However, in patients with eGFR < 60 ml/min, according to previous studies and the post-hoc analysis that we performed, it is probably advisable to stop the AngII blockade at least 24 hours before exposure to contrast media. More prospective studies should be conducted to investigate the optimal duration of temporary cessation of ACE-I and ARB before and after coronary angiography.

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Capsule

Human MX2 is an interferon-induced post-entry inhibitor of HIV-1 infection

Animal cells harbor multiple innate effector mechanisms that inhibit virus replication. For the pathogenic retrovirus human immunodeficiency virus type 1 (HIV-1), these include widely expressed restriction factors, such as APOBEC3 proteins, TRIM5-α, BST2 and SAMHD1, as well as additional factors that are stimulated by type 1 interferon (IFN). Goujon and co-authors used both ectopic expression and gene-silencing experiments to define the human dynamin-like, interferon (IFN)-induced myxovirus resistance 2 (MX2, also known as MXB) protein as a potent inhibitor of HIV-1 infection and as a key effector of IFNα-mediated resistance to HIV-1 infection. MX2 suppresses infection by all HIV-1 strains tested, has equivalent or reduced effects on divergent simian immunodeficiency viruses, and does not inhibit other retroviruses such as murine leukemia virus. The Capsid region of the viral Gag protein dictates susceptibility to MX2, and the block to infection occurs at a late post-entry step, with both the nuclear accumulation and chromosomal integration of nascent viral complementary DNA suppressed. Finally, human MX1 (also known as MXA), a closely related protein that has long been recognized as a broadly acting inhibitor of RNA and DNA viruses, including the orthomyxovirus influenza A virus, does not affect HIV-1, whereas MX2 is ineffective against influenza virus. MX2 is therefore a cell-autonomous, anti-HIV-1 resistance factor whose purposeful mobilization may represent a new therapeutic approach for the treatment of HIV/AIDS.

Nature 2013; 502: 559

Eitan Israeli

Capsule

Temperature triggers immune evasion by *Neisseria meningitidis*

Neisseria meningitidis has several strategies to evade complement-mediated killing, and these contribute to its ability to cause septicemic disease and meningitis. However, the Meningococcus is primarily an obligate commensal of the human nasopharynx, and it is unclear why the bacterium has evolved exquisite mechanisms to avoid host immunity. Loh and colleagues demonstrate the mechanisms of meningococcal immune evasion and resistance against complement increase in response to an increase in ambient temperature. The authors identified three independent RNA thermosensors located in the 5′ untranslated regions of genes necessary for capsule biosynthesis, the expression of factor H binding protein, and sialylation of lipopolysaccharide, which are essential for meningococcal resistance against immune killing. Therefore, increased temperature (which occurs during inflammation) acts as a 'danger signal' for the Meningococcus, enhancing its defense against human immune killing. Infection with viral pathogens, such as influenza, leads to inflammation in the nasopharynx with an increased temperature and recruitment of immune effectors. Thermoregulation of immune defense could offer an adaptive advantage to the Meningococcus during co-infection with other pathogens and promote the emergence of virulence in an otherwise commensal bacterium.

Nature 2013; 502: 237

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