

Behind the Scenes of Adherence in a Minority Population

Uri Yoel MD^{1,2}, Talab Abu-Hammad MD³, Arnon Cohen MD^{1,5}, Alexander Aizenberg MD³, Daniel Vardy MD^{1,4} and Pesach Shvartzman MD^{1,3}

¹Siaal Research Center for Family Medicine and Primary Care, Department of Family Medicine, Division of Community Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

²Department of Internal Medicine A, Soroka University Medical Center, Beer Sheva, Israel

³Clalit Health Services, South District, Beer Sheva, Israel

⁴Leumit Health Services, Central Management, Tel Aviv, Israel

⁵Chief Physician Office, General Management, Clalit Health Services, Tel Aviv, Israel

ABSTRACT: **Background:** The rate of adherence to treatment for diabetes mellitus (DM), hypertension (HTN) and lipid metabolic disorder (LMD) is significantly lower in the Bedouin population compared with the Jewish population in southern Israel. **Objectives:** To investigate the reasons for non-adherence associated with cardiovascular risk factors among Bedouins. **Methods:** We identified Bedouin patients with HTN, DM or LMD from medical records and randomly selected 443 high adherent and 403 low adherent patients. Using trained interviewers we conducted in-depth structured interviews regarding knowledge and attitudes to chronic illness and its treatment, health services evaluation, and socio-demographic factors. **Results:** The study population included 99 high and 101 low adherent patients. More low adherent patients agreed that traditional therapy can replace prescribed medications for DM, HTN or LMD (47% vs. 26%, $P < 0.01$), and 10% used only traditional medications. Also, more low adherent patients believed that the side effects of prescribed drugs are actually worse than the disease itself (65% vs. 47%, $P < 0.05$), and 47% cited this as a reason for discontinuing drug treatment (47% vs. 31%, $P < 0.05$). **Conclusions:** Our findings suggest that in this minority population the basis for non-adherence derives directly from patients' perceptions of chronic disease and drug treatment. A focused intervention should emphasize the importance of early evidence-based drug therapy with open patient-physician dialogue on the meaning of chronic disease and the side effects of prescribed drugs.

IMAJ 2013; 15: 17–22

KEY WORDS: Bedouins, chronic illness, cardiovascular diseases, adherence

Chronic diseases, especially cardiovascular diseases, are neglected globally despite growing awareness of the serious burden they impose [1]. In contrast to the decreased rates in morbidity and mortality from CVD in western countries

over the last three decades, in developing countries CVD morbidity rates were found to increase with urbanization, modernization and the abandonment of traditional lifestyles [2]. Thus, some minority populations in developed countries tend to demonstrate increased prevalence of CVD risk factors more typically seen in the developing world, resulting in higher overall CVD morbidity and mortality in these groups [3].

The Bedouins in the Negev are a population in rapid transition from a traditional nomadic to a western sedentary lifestyle that has led to substantial changes in dietary habits and decreased physical activity and subsequent changes in morbidity patterns [4]. Early surveys among Bedouins conducted 50 years ago found few patients with hypertension and diabetes mellitus and none with ischemic heart disease [5,6]. Hospitalization data in the Negev district during the years 1994–1998 show an increase in hospitalizations due to myocardial infarction and stroke among Bedouins; this rate diverges from trends in the neighboring Jewish towns [7]. A retrospective analysis of in-hospital data of 352 patients admitted with a first acute MI during the period 1997–2003 to Soroka Medical Center found no differences in the clinical characteristics and in-hospital management of patients with acute MI between Bedouins residing in permanent villages versus unrecognized villages (village settlements not recognized by the Israeli government) [8].

A recent study assessing adherence to drug treatment for CVD risk factors (hypertension, diabetes and lipid metabolic disorder) among Negev Bedouins in comparison with the Jewish population found significantly lower adherence rates in the Bedouin population, with 67% of the hypertensive and 73% of the diabetic Bedouin patients not adhering to treatment [9]. Several other studies have consistently demonstrated lower adherence patterns to treatment for chronic diseases among minority populations in the developed world when compared with the general local population [3,10–12].

Non-adherence to cardiovascular medications is a significant problem that has a negative effect on clinical outcome

[13]. The alarmingly low adherence rates to drug therapy among Bedouins with cardiovascular risk factors should be a call to action for the design and implementation of appropriate interventions. This study was designed to evaluate the reasons for non-adherence in the Bedouin population – with at least one of the cardiovascular risk factors: diabetes, hypertension and lipid metabolic disorder – using in-depth personal interviews of adherent and non-adherent Bedouin patients.

METHODS

SETTING

Approximately 170,000 Bedouins live in the Negev region, the majority residing in eight Bedouin towns, others in small and unrecognized villages and a small minority who remain semi-nomadic [14]. The present study was conducted in the eight largest Bedouin primary care clinics in the Negev, which serve most of the Bedouin Negev population. These clinics belong to Clalit Health Services, Southern District. Clalit is the largest of Israel's four health management organizations and the major health services provider for the Bedouin population.

STUDY POPULATION

All computerized medical records of 28,449 Clalit members aged 20 and above listed in the eight main Clalit clinics located in the Bedouin towns were screened for at least one of the following cardiovascular risk factors: hypertension, diabetes and lipid metabolic disorder, and 5625 patients (19.7%) were identified. During the period June 2005 to May 2006, annual prescription purchasing data were obtained for each patient in the study population, including anti-hypertensive, anti-glycemic and lipid-lowering drugs. This information was extracted from the pharmacy's mainframe database.

STUDY SAMPLE

High adherence patients were defined as those with ≥ 9 months of drug purchasing during a calendar year of all prescribed drugs for diabetes, hypertension and lipid metabolic disorder (1183 patients), and low adherence patients as those with ≤ 4 months of drug purchasing during a calendar year (722 patients). From these two groups, 403 patients with low adherence and 443 patients with high adherence were randomly chosen. The patients were sampled in proportion to the catchment area of the population served in each of the eight study clinics.

STUDY TOOLS

The main study tool was a structured questionnaire, which was designed and validated using acceptable research methods. We conducted a review of the medical literature regarding the reasons for non-adherence. A series of four focus groups were held comprising Bedouin patients with chronic

disease, administrative and management staff, and physicians and nurses working within the Bedouin population to determine the potential variables that influenced adherence to medical treatment in this unique population. The focus groups used a "nominal group learning" approach. Each participant wrote down reasons for non-adherence according to his/her opinion. After all potential reasons were compiled, close variables were combined and irrelevant variables were deleted. Each group participant assigned a score from 1 (low) to 5 (high) to each variable according to its perceived significance. High score reasons for non-adherence were then added to the questionnaire which was constructed based on analyses of these focus group findings and the relevant literature. The questionnaire was translated and validated into Arabic using the double-translation method [15]. The questionnaire was then pilot tested and cultural and language modifications were implemented.

DATA COLLECTION

During 2007, patients included in the study were personally interviewed in their home or in the clinic according to their preference using the structured questionnaire. The questionnaire included: knowledge and attitudes to chronic illness and its treatment, medications and medical services used, health services evaluation and ease of accessibility, in addition to socio-demographic details. The interviews were carried out by professionally trained Arabic-speaking interviewers. The study received approval from the local Institutional Review Board Committee.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS-11.5). The correlation between adherence and multiple variants according to the results of the questionnaires was evaluated. Chi-square tests were used to analyze statistically significant differences between categorical variables. Continuous variables were analyzed using an independent *t*-test. Two-sided *P* values ≤ 0.05 were considered statistically significant with 80% power for all analyses.

RESULTS

COHORT SOCIO-DEMOGRAPHIC CHARACTERISTICS

The study population included 101 low and 99 high adherent patients. Table 1 describes the socio-demographic characteristics of the study population. Patients in the high adherence group were older (55 ± 12 vs. 50 ± 12 , $P < 0.001$), female (64% vs. 49%, $P < 0.01$), and were socioeconomically stronger in comparison with low adherent patients. No difference in terms of accessibility to medical services was found between the two groups ($P = 0.32$).

MORBIDITY AND KNOWLEDGE ABOUT COMPLICATIONS

We compared morbidity patterns and knowledge about complications of diabetes, hypertension and lipid metabolic disorder. The low adherent group included more patients with lipid metabolic disorder as the single risk factor (30% vs. 5%, $P < 0.0001$), whereas the high adherence group included more patients with diabetes (66% vs. 33%, $P < 0.0001$) and hypertension (71% vs. 50%, $P < 0.0001$). Knowledge questions were expressed simply (e.g., “vision loss,” “damage to kidneys,” etc.) without using professional terms. For most listed complications, less than 50% of patients from both groups could identify the main complications of their illness [Table 2].

PATIENTS’ PERCEPTIONS OF CHRONIC DISEASE AND ITS TREATMENT

In both groups (high and low adherence), more than 75% of diabetic patients, 88% of hypertensive patients and 85% of patients with lipid metabolic disorder had been advised to use a specific drug to manage their chronic disease/s and 95% of them purchased their drugs in the Clalit pharmacies ($P = 0.85$). More than 55% of all patients believed that diabetes, hypertension and lipid metabolic disorder are diseases that could be cured and that in the future no drug treatment would be needed ($P = 0.89$). Over 85% of patients claimed that a drug treatment for these diseases would result in cure ($P = 0.08$). Several questions dealt with the self-image of a patient with a chronic disease. Low adherent patients tended to agree more with statements that drew a negative picture of chronic diseases; 30% of these patients agreed that “when a patient is newly diagnosed with diabetes, hypertension and lipid metabolic disorder, it is a sign for him that he is approaching the end of his life” (30% vs. 25%, $P < 0.05$). More low adherent patients believed that “since a patient is found to have a chronic disease, his family members and friends start looking at him differently” (59% vs. 46%, $P = 0.07$).

Table 3 presents patients’ perceptions of drug treatment and traditional therapy. More low adherent patients agreed that “traditional drugs can sometimes replace the treatment given by physicians for diabetes, hypertension and lipid metabolic disorder” (47% vs. 26%, $P < 0.01$), and 10 (10%) (none of the high adherent patients) actually used traditional medicine instead of prescribed drugs. More low adherent patients believed that “the side effects of prescribed drugs may be worse than the disease that they are intended to treat” (65% vs. 47%, $P < 0.05$). Seventy percent of patients in both groups believed that “prescribed drugs include harmful chemicals” ($P = 0.43$) and many reported that they discontinued to use a specific drug for diabetes, hypertension and lipid metabolic disorder because of its side effects (47% vs. 31%, $P < 0.05$, low and high adherence respectively).

PATIENT RELATIONSHIPS WITH MEDICAL PROFESSIONALS

Over 55% of all patients declared that their physicians could express themselves fluently in Arabic ($P = 0.21$) and over 60%

Table 1. Socio-demographic characteristics of the study population

Variables		Low adherence (N=101)		High adherence (N=99)		P value
		n	%	n	%	
Age (yrs)	Average ± SD	49.7 ± 12		55.3 ± 12.4		< 0.001
	Range	22–77		28–82		
Gender	Male	52	51.5%	36	36.4%	< 0.01
	Female	49	48.5%	63	63.6%	
Marital status	Married	86	85.1%	73	73.7%	< 0.05
	Not married	15	14.8%	26	26.3%	
Economically dependent children	Average ± SD	5.8 ± 4.8		4.4 ± 4.2		< 0.05
	Range	0–23		0–16		
Children < age 18	Average ± SD	4 ± 4.1		2.8 ± 3.1		< 0.05
	Range	0–18		0–14		
Living density (no. of persons/room)	Average ± SD	1.95 ± 1.2		1.5 ± 0.85		< 0.01
	Range	0.25–6.5		0.25–4.3		
Persons sharing monthly income	Average ± SD	7 ± 4.7		5.9 ± 4.5		0.09
	Range	0–24		0–27		
Monthly family’s drug expense (NIS)	Average ± SD	242 ± 308		170 ± 193		0.05
	Range	0–1500		0–700		

SD = standard deviation, NIS = new Israeli Shekel (equivalent of 25 U.S. cents)

Table 2. Knowledge of disease complications

Disease	Adherence	Knowledge of possible complications* of diabetes, hypertension and lipid metabolic disorder					Total
		Vision loss	Renal failure	Amputation	IHD	Stroke	
Diabetes	Low N (%)	23 (69.7)	10 (30.3)	15 (45.4)	8 (24.2)	8 (24.2)	33
	High N (%)	47 (72.3)	17 (26.1)	31 (47.7)	15 (23.1)	6 (9.2)	65
	Pvalue	< 0.0001	0.66	0.83	0.9	< 0.05	-
Hypertension	Low N (%)	23 (45.1)	1 (2)	Irr	20 (39.2)	10 (19.6)	51
	High N (%)	42 (60)	10 (14.3)	Irr	25 (35.7)	11 (15.7)	70
	Pvalue	< 0.01	< 0.01	Irr	0.69	0.58	-
Lipid metabolic disorder	Low N (%)	Irr	Irr	Irr	40 (62.5)	12 (18.7)	64
	High N (%)	Irr	Irr	Irr	26 (46.3)	11 (19.6)	56
	Pvalue	Irr	Irr	Irr	< 0.05	0.9	-

*Only major complications are shown
IHD = ischemic heart disease, Irr = Irrelevant

of patients stated that they themselves could understand at least simple explanations in Hebrew ($P = 0.08$). Over 75% of all patients felt that “when they were newly diagnosed with diabetes, hypertension and lipid metabolic disorder they were well informed about their disease, its complications and options of drug therapy” ($P = 0.91$). Questions aimed to investigate the relationship between patients and medical staff consistently established that more than 80% of all patients felt comfort-

Table 3. Patients' perceptions of drug treatment and traditional therapy

Statements	Degree of agreement	Low adherence (n=101)		High adherence (n=99)		P value
		N	%	N	%	
Traditional drugs can sometimes replace prescribed drugs for diabetes, hypertension and lipid metabolic disorder	Agree	47	46.5%	26	26.3%	< 0.01
	Don't agree	36	35.6%	56	56.6%	
	Don't know	18	17.8%	17	17.2%	
Traditional drugs are safer and have fewer side effects than prescribed drugs	Agree	57	56.4%	42	42.2%	0.08
	Don't agree	21	20.8%	32	32.3%	
	Don't know	23	22.8%	25	25.2%	
Patients with diabetes, hypertension and lipid metabolic disorder can be cured with traditional drugs	Agree	41	40.6%	24	24.2%	< 0.05
	Don't agree	36	35.6%	48	48.5%	
	Don't know	24	23.8%	27	27.3%	
Prescribed drugs contain harmful chemicals	Agree	71	70.3%	69	69.7%	0.43
	Don't agree	19	18.8%	14	14.1%	
	Don't know	11	10.9%	16	16.2%	
Most patients using prescribed drugs suffer from its side effects*	Agree	66	66%	53	53.5%	0.06
	Don't agree	27	27%	29	29.3%	
	Don't know	7	7%	17	17.2%	
Prescribed drugs' side effects are graver than the diseases they are intended to treat*	Agree	56	56%	47	47.5%	< 0.05
	Don't agree	28	28%	21	21.2%	
	Don't know	16	16%	31	31.3%	
I stopped a prescribed drug for diabetes, hypertension and lipid metabolic disorder because of side effect*	Agree	47	47%	31	31.3%	< 0.05
	Don't agree	45	45%	50	50.5%	
	Don't know	8	8%	18	18.2%	

*Only 100 low adherent patients answered this question

able to address clinic staff with questions about their disease, its complications, as well as treatment options and their side effects ($P = 0.15$).

DISCUSSION

The present study aimed to explore the root causes of low adherence to medical treatment among Bedouins with diabetes, hypertension and lipid metabolic disorder in southern Israel using in-depth interviews of patients with both low and high degrees of adherence. Our main findings were as follows

- Patients of both groups exhibited poor knowledge about the main complications of their chronic illness [Table 2]
- Patient's attitudes towards prescribed medications were negative, with 70% believing that drugs contain harmful chemicals
- Most questions regarding patients' perceptions of drug treatment and traditional therapy exhibited statistically significant differences between the two groups [Table 3]. Low adherent patients were more suspicious about prescribed drugs, with 47% of them noting that they stopped

treatment due to what they perceived as side effects

- While most patients did not except the concept of chronic diseases, believing instead that the conditions could be cured, low adherent patients were more likely to articulate the negative effect of chronic diseases on their own life
- The morbidity patterns of low adherent patients differed from those of high adherent patients. Most low adherent patients tended to have only one disease that was less symptomatic. Conversely, most high adherent patients had more than one disease and 66% of them were diabetics
- More than 80% of all patients reported positive feelings with regard to the clinic staff and their doctors.

In contrast to previous adherence studies that used focus groups as their principle means of data collection and were largely qualitative in nature, the study design in the present study used in-depth interviews based on a structured questionnaire. This enabled us to evaluate the possible causes of non-adherence in a quantitative manner. Because study participants' medical records and drug purchasing data were computerized, and 95% of all patients purchased their drugs

in Clalit pharmacies, we believe that the study sample truly represents high and low adherent patients in the Bedouin population. Nevertheless, the study had several limitations:

- Since only a quarter of the randomly chosen patients were interviewed, there is a potential selection bias in the results of our study. However, we assume that this bias was applied equally to both groups
- A questionnaire-based study may be biased by the interviewers; however, since high and low adherent patients were interviewed by the same professionally trained Arabic-speaking interviewers, we believe that this potential bias was minimized as much as possible
- Most interviews took place in the clinics. The fact that more than 80% of patients answered positively when asked about their relationship with the clinical team raises questions about whether or not the location of the interview played a role in introducing response bias into this assessment. Although confidentiality was promised and maintained, we cannot rule out this bias with certainty.

Previous studies addressing adherence in minority populations found that factors such as younger age, lower education and socioeconomic status, fear of side effects, and asymptomatic diseases were closely associated with low adherence. The findings of these studies emphasized poor patient-physician interaction as a principle factor for non-adherence [16-18]. In contrast, patient-physician interaction was not the main explanation for non-adherence in our study, as more than 80% of all patients reported positive feelings with regard to clinic medical staff. However, indirect questions point to the possibility that barriers in patient-physician communication may play a partial role in this setting as well. Low adherent patients in the present study were younger than high adherent patients. The correlation between young age and low adherence was found in other studies on this issue [3,17,19,20]. Thus, it can be suggested that younger patients in general are more reluctant to view themselves as chronically ill patients – a possible significant factor in regular adherence to drug therapy.

The correlation between the concurrent co-morbidities and symptoms of chronic diseases and better adherence is a common finding in adherence studies [18-20]. In the present study, patients were not asked about their symptoms. We believe that high adherent patients were more symptomatic without proper drug therapy due to the fact that they were more likely to have diabetes and co-morbidities, which in turn encouraged them to be more adherent.

Our findings suggest that the basis for non-adherence derives from patient perceptions of chronic disease and drug treatment in this minority population. As Bedouins move to an increasing western sedentary lifestyle, knowledge and attitudes regarding chronic disease have yet to match the high

prevalence chronic disease found in the Bedouin community. This suggests that high adherent patients are often those whose perception of chronic diseases more closely matches the “western” framework of health care service delivery, while low adherent patients are more closely assigned to the traditional treatment options. Although the study was performed 5 years ago, physicians treating this minority population still feel there are non-adherent Bedouin patients with diabetes, hypertension and lipid metabolic disorder.

The insights of the present study provide a strong foundation on which to plan a focused intervention aimed at creating change among non-adherent Bedouin patients with these disorders. Patients should be informed in a routine manner of the complications of their chronic diseases, and the importance of early evidence-based drug therapy should be emphasized. Patient fears of side effects should be addressed openly by physicians. This information should be communicated in Arabic or with proper translation.

The results of the present study pose two essential questions. First, is a change in perception in such a traditional community possible? Second, can the insights emerging from the present study be used as the basis for intervention among other minority populations? We believe that the answer to both questions is yes, though since perception might be hard to change, significant increases in both medical and educational resources will be needed. A focused intervention among low adherent Bedouin patients with cardiovascular risk factors should be the next step with a follow-up study aimed to evaluate its efficacy.

Acknowledgments

The study was supported by a grant from The National Institute for Health Policy Research

Corresponding author:

Dr. P. Shvartzman

Head, Dept. of Family Medicine, Division of Community Health, Ben-Gurion University of the Negev, P.O. Box 653, Beer Sheva 84105, Israel

Phone: (972-8) 647-7429

Fax: (972-8) 647-7636

email: spesah@bgu.ac.il

References

1. Geneau R, Stuckler D, Stachenko S, et al. Raising the priority of preventing chronic diseases: a political process. *Lancet* 2010; 376: 1689-98.
2. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998; 97: 596-601.
3. Mochari H, Ferris A, Adigopula S, Henry G, Mosca L. Cardiovascular disease knowledge, medication adherence, and barriers to preventive action in a minority population. *Prev Cardiol* 2007; 10: 190-5.
4. Cohen AD, Gefen K, Ozer A, et al. Diabetes control in the Bedouin population in southern Israel. *Med Sci Monit* 2005; 11: CR376-80.
5. Ben Assa S. The medical work among the Bedouins in the Negev. *Harefuah* 1961; 61: 211-12 (Hebrew).
6. Ben Assa S. Observation on 2000 Bedouin patients. *Harefuah* 1961; 67: 450-3 (Hebrew).
7. Weitzman S, Rosen S. Report of the working group on “Health Needs of the

- Negev Population.” The Goldman Foundation, 2001.
8. Abu-Tailakh M, Weitzman S, Henkin Y. Risk factors and outcome of acute myocardial infarction in Bedouins living in permanent compared to unrecognized villages in southern Israel. *IMAJ Isr Med Assoc J* 2011; 13 (6): 345-9.
 9. Tamir O, Peleg R, Dreier J, et al. Cardiovascular risk factors in the Bedouin population: management and adherence. *IMAJ Isr Med Assoc J* 2007; 9: 652-5.
 10. Amin AP, Mukhopadhyay E, Nathan S, Napan S, Kelly RF. Association of medical nonadherence and long-term adverse outcome, after myocardial infarction in a minority uninsured population. *Transl Res* 2009; 154: 78-89.
 11. Fernandez S, Scales KL, Pineiro JM, Schoenthaler AM, Ogedegbe G. A senior center-based pilot trial of the effect of lifestyle intervention on blood pressure in minority elderly people with HTN. *J Am Geriatr Soc* 2008; 56: 1860-6.
 12. Perez-Stable EJ, Salazar R. Issues in achieving adherence with antihypertensive treatment in a Latino population. *Clin Cornerstone* 2004; 6: 49-61.
 13. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of adherence and persistence in the treatment of diabetes, HTN and LMD: a review. *Int J Clin Pract* 2008; 62: 76-87.
 14. Statistical Yearbook of the Negev Bedouin 2004. Beer Sheva: The Center for Bedouin Studies and Development & the Negev Center for Regional Development, Ben-Gurion University of the Negev (Hebrew).
 15. Sperber AD, DeVellis RF, Boehlecke B. Cross-cultural translation: methodology and validation. *J Cross-Cult Psychol* 1994; 25: 501-24.
 16. Gascón JJ, Sanchez-Ortuno M, Llor B, Skidmore D, Saturno PJ. Treatment adherence in HTN study group. Why hypertensive patients do not comply with the treatment: results from a qualitative study. *Fam Pract* 2004; 21: 125-30.
 17. Lukoschek P. African Americans' beliefs and attitudes regarding hypertension and its treatment: a qualitative study. *J Health Care Poor Underserved* 2003; 14: 566-87.
 18. McLane CG, Zyzanski SJ, Flocke SA. Factors associated with medication nonadherence in rural elderly hypertensive patients. *Am J Hypertens* 1995; 2: 206-9.
 19. Taira DA, Gelber RP, Davis J, Gronley K, Chung RS, Seto TB. Antihypertensive adherence and drug class among Asian Pacific Americans. *Ethn health* 2007; 12: 265-81.
 20. Lee R, Taira DA. Adherence to oral hypoglycemic agents in Hawaii. *Prev Chronic Dis* 2005; 2 (2): A09. Epub 2005 Mar 15.

Capsule

A vaccine strategy that protects against genital herpes by establishing local memory T cells

Most successful existing vaccines rely on neutralizing antibodies, which may not require specific anatomical localization of B cells. However, efficacious vaccines that rely on T cells for protection have been difficult to develop, as robust systemic memory T cell responses do not necessarily correlate with host protection. In peripheral sites, tissue-resident memory T cells provide superior protection compared to circulating memory T cells. Shin et al. describe a simple and non-inflammatory vaccine strategy that enables the establishment of a protective memory T cell pool within peripheral tissue. The female genital tract, which is a portal of entry for sexually transmitted infections, is an immunologically restrictive tissue that prevents entry of activated T cells in the absence of inflammation or infection. To overcome this obstacle, the authors developed a vaccine strategy that they

term “prime and pull” to establish local tissue-resident memory T cells at a site of potential viral exposure. This approach relies on two steps: conventional parenteral vaccination to elicit systemic T cell responses (prime), followed by recruitment of activated T cells by means of topical chemokine application to the restrictive genital tract (pull), where such T cells establish a long-term niche and mediate protective immunity. In mice, prime and pull protocol reduces the spread of infectious herpes simplex virus 2 into the sensory neurons and prevents development of clinical disease. These results reveal a promising vaccination strategy against herpes simplex virus 2, and potentially against other sexually transmitted infections such as human immunodeficiency virus.

Nature 2012; 491: 463

Eitan Israeli

Capsule

A FOXO3-IRF7 gene regulatory circuit limits inflammatory sequelae of antiviral responses

Antiviral responses must be tightly regulated to defend rapidly against infection while minimizing inflammatory damage. Type 1 interferons (IFN-I) are crucial mediators of antiviral responses and their transcription is regulated by a variety of transcription factors; principal among these is the family of interferon regulatory factors (IRFs). The IRF gene regulatory networks are complex and contain multiple feedback loops. The tools of systems biology are well suited to elucidate the complex interactions that give rise to precise coordination of the interferon response. Litval et al. have used an unbiased systems approach to predict that a member of the forkhead family of transcription factors, FOXO3, is a negative regulator of a subset of antiviral genes.

This prediction was validated using macrophages isolated from Foxo3-null mice. Genome-wide location analysis combined with gene deletion studies identified the Irf7 gene as a critical target of FOXO3. FOXO3 was identified as a negative regulator of Irf7 transcription and they have further demonstrated that FOXO3, IRF7 and IFN-I form a coherent feed-forward regulatory circuit. These data suggest that the FOXO3-IRF7 regulatory circuit represents a novel mechanism for establishing the requisite set points in the interferon pathway that balances the beneficial effects and deleterious sequelae of the antiviral response.

Nature 2012; 490: 421

Eitan Israeli