GENETIKA RESISTENCE K ONEMOCNĚNÍM

RESISTENCE

- ***Druhová***
- ***Plemenná***
- ***Individuální:***

- obecná
- specifická

Meziplemenné rozdíly

Mammalian breeds reported to DAD-IS as having resistance or tolerance to specific diseases or parasites

Disease	Buffalo	Cattle	Goat	Sheep	Pig	Horse	Deer
Trypanosomiasis		17	4	4			
Tick infestation/burden	1	17		1			1
Tick-borne diseases (unspecified)		4					
Anaplasmosis		2					
Piroplasmosis/Babesiosis		4				1	
Heartwater/Cowdriosis		1		1			
Internal parasites/worms	1	2	1	9	1	2	1
Fascioliasis	2			1			
Bovine leukosis		9					
Foot rot (*Bacteroides nodusos*)		1		14			
Total*	4	59	6	33	3	5	2

*Total number of entries related to disease resistance or tolerance (some breeds are reported to show resistance or tolerance to more than one disease).

http://www.fao.org/docrep/010/a1250e/a1250e00.htm

Meziplemenné rozdíly

Breeds reported to DAD-IS as showing resistance or tolerance to tick-borne diseases

Species/Subregion	Disease	Number of breeds	Most common name of breed
Cattle			
North & West Africa	Tick-borne diseases (unspecified)	2	Baoulé, Ghana Shorthorn
Southern Africa	Tick-borne diseases (unspecified)	1	Angoni (2)
Europe & the Caucasus	Anaplasmosis	2	Cinisara, Modicana,
North & West Africa	Piroplasmosis	2	N'dama, Noire Pie de Meknès
Europe & the Caucasus	Piroplasmosis	1	Modicana
Europe & the Caucasus*	Heartwater (Cowdriosis)	1	Creole (also dermatophilosis)
Sheep			
Southern Africa	Heartwater (Cowdriosis)	1	Damara (2)
Horse			
Europe & the Caucasus	Piroplasmosis	1	Pottok

Figures in parenthesis = number of countries reporting if more than one.
Note that there may be other breeds for which there is evidence of disease resistance or tolerance but for which this has not been reported to DAD-IS.
*Guadeloupe, Martinique.

http://www.fao.org/docrep/010/a1250e/a1250e00.htm

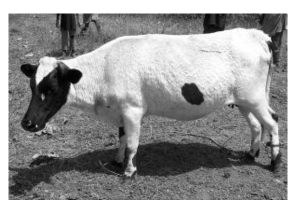
Meziplemenné rozdíly

Breeds reported to DAD-IS as showing resistance or tolerance to internal parasites

Species/Subregion	Number of breeds	Most common name of breed
Cattle		
Southern Africa	1	Madagascar Zebu
Southeast Asia	1	Javanese Zebu
Goat		
Near & Middle East	1	Yei goat
Sheep		
Southern Africa	2	Madgascar, Kumumawa
Southeast Asia	3	Garut, Malin, Priangan
Europe & the Caucasus	1*	Churra Lebrijana (fascioliasis)
Latin America & the Caribbean	3	Criollo (8), Criollo Mora, Morada Nova
Near & Middle East	1	Rahmani
Buffalo		
Southeast Asia	3*	Papua New Guinea Buffalo, Kerbau-Kalang (fascioliasis), Kerbau Indonesia (fascioliasis)
Pig		
Southeast Asia	1	South China
Deer		
Southeast Asia	1	Sambar
Horse		
Southeast Asia	2	Kuda Padi , Bajau

http://www.fao.org/docrep/010/a1250e/a1250e00.htm

Meziplemenné rozdíly

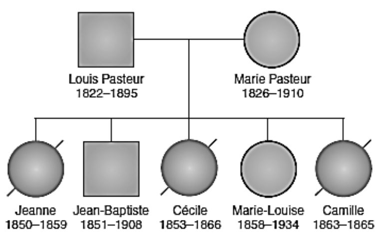


PODSTATA RESISTENCE

Variabilita v reakci na patogenní agens:

Interakce hostitele a patogena

Genetika vnímavosti k infekcím



From: Quintana-Murci et al. Nat Immunol 2007

Genetic resistance and tolerance

as defined by Doeschl/Wilson & Kyriazakis (2012)

****Resistance**: ability to reduce pathogen replication in the host*

vs.

****Tolerance**: ability to maintain homeostasis in the presence of replicating pathogen*

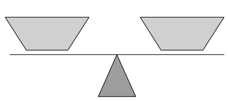
* *Difficult to uncoupling them*
Different genes may be involved

Scylla and Charybdis of immune responses: genetic variation

The dilemma:
too high/too low immune responses?

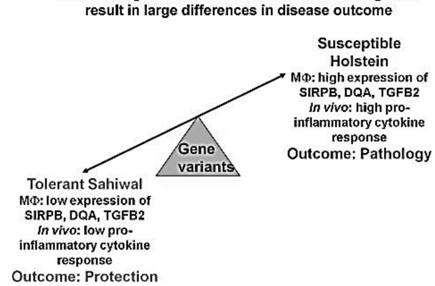
Protective immunity
Resistance to infection

Autoimmunity
Inflammation



Resistance vs. tolerance

Small changes in disease resistance/tolerance genes: result in large differences in disease outcome



Glass et al. Vet Immunol Immunopathol 2012

Mendelistická dědičnost

- Major effects
- Expected to result from low-frequency variants
- Less knowledge than for complex traits

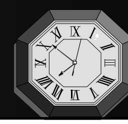
Mendelian disorders of immunity to infection associated with predisposition or resistance to specific infections

Infectious agent	Clinical phenotype	Immunological phenotype	Gene
Neisseria	Invasive disease	MAC deficiency	*C5, C6, C7, C8A, C8B, C8G, C9*
	Invasive disease	Properdin deficiency	*PFC*
Mycobacteria	MSMD Disseminated tuberculosis	IL-12/23–IFN-γ deficiency	*IFNGR1, IFNGR2, STAT1, NEMO, IL12B, IL12RB1*
Streptococcus pneumoniae	Invasive disease	IRAK-4 deficiency	*IRAK4*
Epstein-Barr virus	X-linked lymphoproliferative disease	SAP deficiency	*SH2D1A*
Human papillomavirus	Epidermodysplasia verruciformis	EVER1 or EVER2 deficiency	*EVER1, EVER2*
Plasmodium vivax	Natural resistance	Lack of receptor for pathogen	*DARC*
Human immunodeficiency virus-1	Natural resistance	Lack of receptor for pathogen	*CCR5*
Norovirus	Natural resistance	Lack of receptor for pathogen	*FUT2*

Picard et al Curr Opin Immunol 2006

MUTACE - EVOLUČNÍ NÁSTROJ PATOGENŮ

- Rozdíly v generačním intervalu
- Rozdíly v dlouhodobých a krátkodobých účincích mutací



UMĚNÍ PŘEŽÍT: PATOGEN

Základ: potenciál <u>genetické variability</u> využité k:

- úniku imunitním mechanismům
- indukci imunosuprese
- aktivní modulaci imunitních reakcí hostitele

OBRANNÉ MECHANISMY HOSTITELE

- Neimunitní: *bariéry, receptory, metabolismus, morfologie, etologie atd.*
- Imunitní: přirozená imunita, specifická imunita

IMUNITA = FYZIOLOGICKÁ FUNKCE

====>

V populaci existuje přirozená variabilita imunitních funkcí (Gaussova křivka)

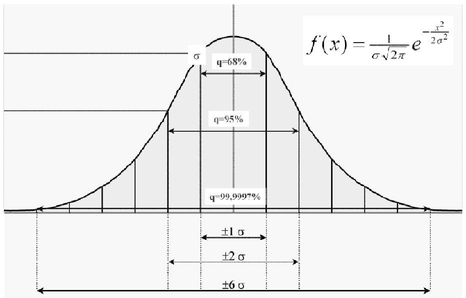
ovlivněná geneticky i prostředím

IMUNITA = KOMPLEX REAKCÍ

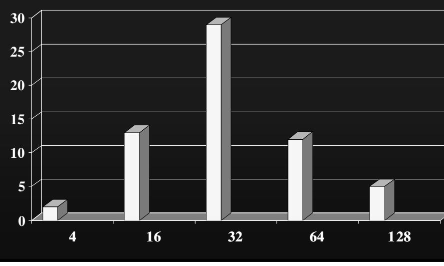
====>

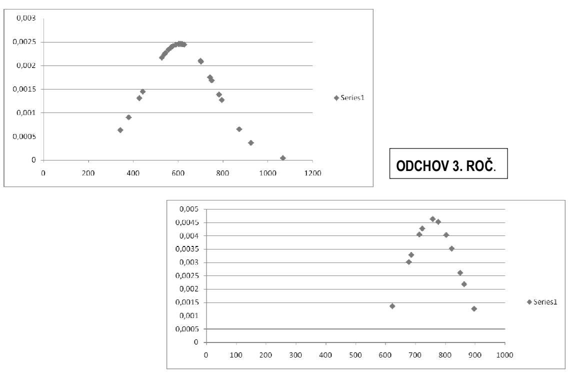
Genetické založení imunitní reaktivity je komplexní - mnohagenové

Gaussovská distribuce



POSTVAKCINAČNÍ TITRY ANTI-EHV-1 NEUTRALIZAČNÍCH PROTILÁTEK (N=61)





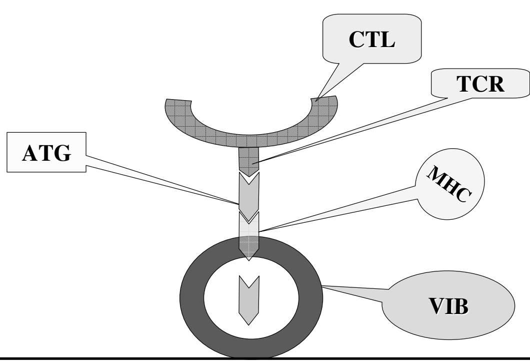
ODCHOV 3. ROČ.

Kmenový plemeník

Příčiny selhání účinku vakcinace proti chřipce

- Druh vakcíny a její kvalita
- Změna viru
- *Nereaktivita hostitele*

PREZENTACE ANTIGENU



DVA TYPY GENŮ IMUNITNÍ ODPOVĚDI

- Zajišťující konkurenceschopnost s variabilitou patogenů: *MHC, TCR, Ig*
- Ostatní: např. *NRAMP*

DVA TYPY GENŮ IMUNITNÍ ODPOVĚDI

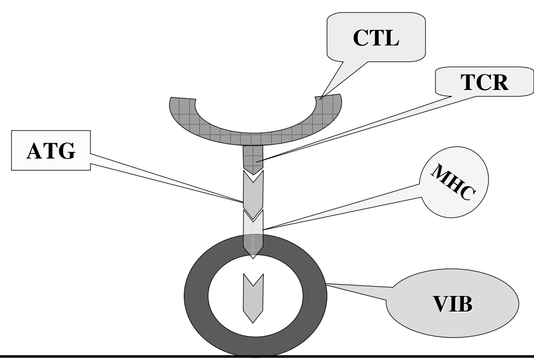
Typ I:

Geny zajišťující konkurenceschopnost s variabilitou patogenů: *MHC, TCR, Ig*

HLAVNÍ HISTOKOMPATIBILITNÍ KOMPLEX - MHC

Molekuly zajišťující prezentaci antigenu imunitnímu systému

PREZENTACE ANTIGENU



HLAVNÍ HISTOKOMPATIBILITNÍ KOMPLEX (MHC)

- *Polymorfismus a heterozygotnost*
- *Vazebná nerovnováha*
- *Asociace s chorobami*

VARIABILITA IG

IDIOTYPOVÁ

- Přestavby DNA pro H a L
- Kombinace H a L
- Alelická exkluze
- Somatické mutace, genová konverze

IR GENY TYPU II

- NRAMP1
- CD (14, 18)
- Cytokiny (TNF, IL, IFN)

IR GENY TYPU II

Příklad mutace: LAD

- **člověk, skot, pes**
- **primární imunodeficience**
- **CD11/18**

Metody kontroly zdravotního stavu zvířat

- Medikamentózní léčba
- Vakcinace
- Eradikace
- Hygiena prostředí, DDD
- Šlechtění na resistenci

INDIKACE K VYUŽITÍ RESISTENCE VE ŠLECHTĚNÍ

- *nepoužitelnost jiných metod*
- *existence dostatečné variability*
- *nezávislost na resistenci k jiným onemocněním a na užitkových vlastnostech*
- *ekonomická efektivnost*

Genetic resistance and tolerance

as defined by Doeschl-Wilson & Kyriazakis (2012)

**Resistance: ability to reduce pathogen replication in the host*

vs.

**Tolerance: ability to maintain homeostasis in the presence of replicating pathogen*

* *Difficult to uncoupling them*
Different genes may be involved

Susceptibility	Tolerance, including carrier status	Resistance

← Non-genetic measures, natural selection, selective breeding →

PŘÍKLADY VYUŽITÍ GENETICKÉ RESISTENCE VE ŠLECHTĚNÍ

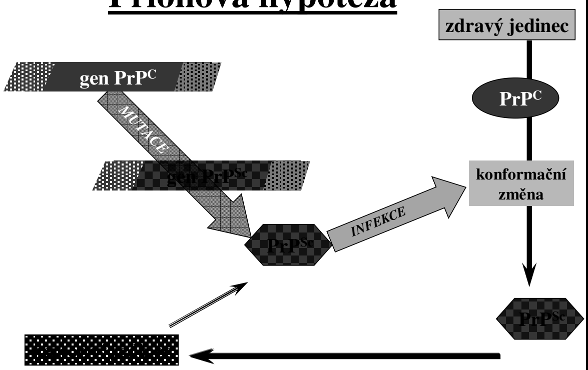
- Skot: mastitidy
- Prase: PSS
- Kur: Markova choroba
- Ovce: scrapie, paraziti GIT

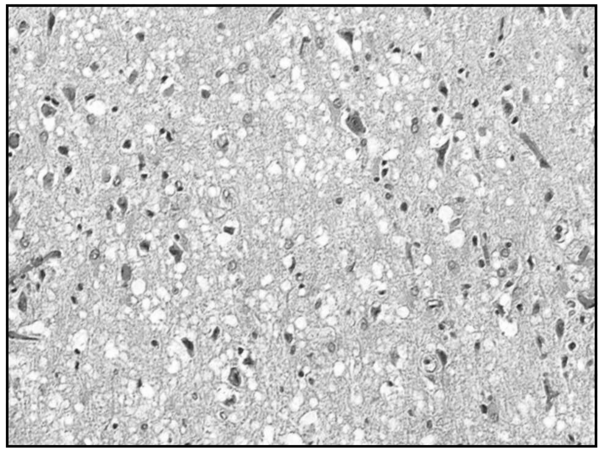
PRIONY, SCRAPIE

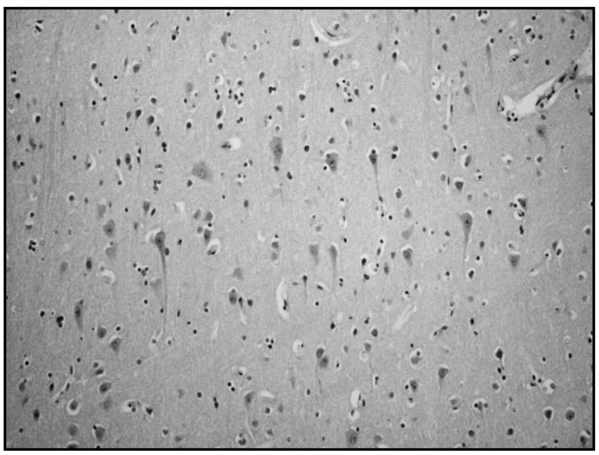
A

GENETICKÁ PODSTATA OZDRAVOVACÍHO PROGRAMU

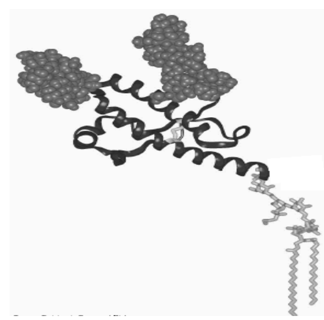
Prionová hypotéza



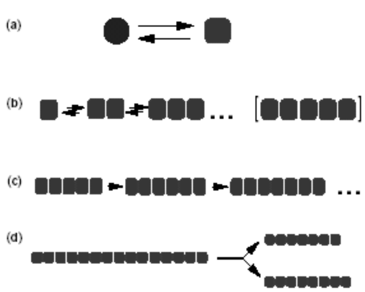




Prionový protein



Vznik prionových částic



PRIONY

Prionový protein

→*PrP^{C}: 33kD, 210 AA,*

40% α–helix - SEN

→*PrP^{Pat}: 45% β–list - RES*

GENETIKA PRIONOVÝCH ONEMOCNĚNÍ

BIOLOGICKÁ ÚLOHA PrP^C (?)

→ Cu^2 homeostáza,

→ Antioxidační procesy

Apoptóza, synaptická homeostáza

OZDRAVOVACÍ PROGRAM

Založen na existenci

GENETICKÉ RESISTENCE KE VZNIKU ONEMOCNĚNÍ

PrP genotypy u ovcí

136	154	171
A	R	R
A	H	Q
A	R	H
A	R	Q
V	R	Q

A = alanin; H = histidin; Q = glutamin; R = arginin; and V = valin

Významné genotypy

ARR / ARR	Sheep that are genetically most resistant to scrapie.
ARR / AHQ ARR / ARH ARR / ARQ	Sheep that are genetically resistant to scrapie, but will need careful selection when used for further breeding.
ARQ / ARH ARQ / AHQ AHQ / AHQ ARH / ARH AHQ / ARH ARQ / ARQ*	Sheep that genetically have little resistance to scrapie but may be sold or used for breeding without restriction until the end of 2004. After this period, any ram on a scheme farm may continue to be used for breeding for a further 3 years (except *), or until the end of its life (whichever the sooner).
ARR / VRQ	Sheep that are genetically susceptible to scrapie but may exceptionally be used for further (controlled) breeding in the context of an approved breeding programme.
AHQ / VRQ ARH / VRQ ARQ / VRQ VRQ / VRQ	Sheep that are highly susceptible to scrapie and must be humanely slaughtered or castrated.

VÝZNAM RESISTENCE VE ŠLECHTĚNÍ

- Zpětnovazebná regulace efektivnosti procesu šlechtění na užitkové vlastnosti
- Indikace biologických mezí genetického pokroku

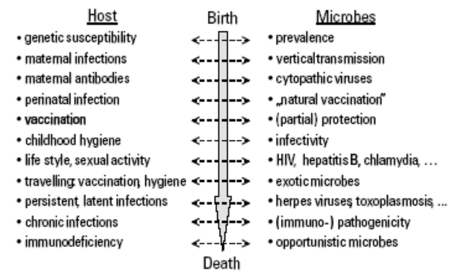
Metody kontroly zdravotního stavu zvířat

- Medikamentózní léčba
- Vakcinace
- Eradikace
- Hygiena prostředí, DDD
- Šlechtění na resistenci

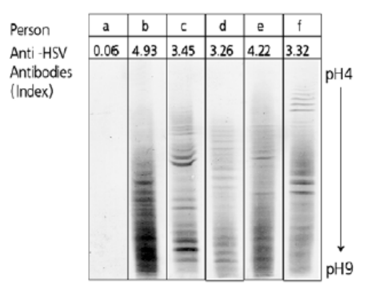
Vakcinace a genetika

- Individuální variabilita imunitní odpovědi po vakcinaci
- Využití genetických principů při produkci nových vakcín, farmakogenomika

Člověk a infekce



Variabilita antiinfekční imunitní odpovědi u člověka



Genetics of vaccination

Table 1. Host mechanisms involved in vaccine-induced immune responses

Function	Genes (examples)
Attachment, entry, replication (live vaccines)	CD150/SLAM
Antigen recognition	Toll-like receptors
Antigen uptake by and activation of innate immune system	HLA class III genes (complement proteins C3 and C4), costimulatory molecules (CD80, CD86), CD21, CD35, killer Ig-like receptors
Antigen processing and presentation	HLA class I/II genes, TAP, CD21, CD35
B/T lymphocyte function	CD40, CD40 ligand, B/T cell receptors, G proteins
Immune regulation	Cytokines, monokines, C-C chemokines (and receptors)
Effector and accessory cell function	Fc receptors

SLAM = Signaling lymphocyte activation molecule, identified as measles virus receptor.

Genetics of vaccination

Table 3. Heritability estimates of vaccination responses in twin studies

Vaccine	Parameter	DZ[a]	MZ[a]	Population	Age	Study	Heritability, %	95% CI %	References
Measles	antibody	55	45	USA[b]	2–18 years	cross-sectional	89	≥ 52[c]	18
Mumps	antibody	55	45	USA[b]	2–18 years	cross-sectional	39	≥ 2[c]	18
Rubella	antibody	55	45	USA[b]	2–18 years	cross-sectional	46	≥ 5[c]	18
HAV	antibody	95	96	Germany	18–65 years	prospective	36	–2–73	15
HBsAg	antibody	95	96	Germany	18–65 years	prospective	61	41–81	15
HBsAg	antibody	159	48	Gambia	5 months	prospective	77	63–85	12[d]
Polio	antibody	159	48	Gambia	5 months	prospective	60	43–73	12
Tetanus	antibody	159	48	Gambia	5 months	prospective	44	16–70	12
Tetanus	IL-13	159	48	Gambia	5 months	prospective	64	50–75	12
Diphtheria	antibody	159	48	Gambia	5 months	prospective	49	17–77	12
Hib	antibody	147	43	Gambia	5 months	prospective	51	32–66	14
Pertussis									
Pertactin	IFN-γ	159	48	Gambia	5 months	prospective	53	35–67	12
FHA	IFN-γ	159	48	Gambia	5 months	prospective	65	50–76	12
Toxin	IL-13	159	48	Gambia	5 months	prospective	57	40–71	12
BCG									
PPD	IFN-γ	159	48	Gambia	5 months	prospective	41	10–71	12
KMTB	IFN-γ	159	48	Gambia	5 months	prospective	39	3–71	12
PPD	IL-13	159	48	Gambia	5 months	prospective	46	5–75	12
Hsp65	IL-13	159	48	Gambia	5 months	prospective	50	29–67	12

HLA a spalničky

Associations between HLA gene polymorphisms and humoral (IgG antibody) and cellular (lymphoproliferation) immune responses to measles vaccine

HLA gene	Variant	Effect	References
Class I allele	B*8, B*13, B*44	Decreased antibody (single dose)	[14]
Class I allele	B*7	Increased antibody (single dose)	
Class II allele	DRB1*03, DQA1*0201	Decreased antibody (single dose)	[15]
Class II allele	DRB1*08, DQA1*0104, DPA1*0202	Increased antibody (single dose)	[16]
Class I supertype	B7	Increased antibody (two doses)	[17]
Class I supertype	B44	Decreased antibody (two doses)	
Class I supertype	B58	Decreased antibody (two doses)	
Class I haplotype	A*24-C*03-B*15	Decreased antibody (two doses)	[18]
Class II haplotype	DRB1*07-DQB1*03-DPB1*04	Decreased antibody (two doses)	[18]
Class II haplotype	DRB1*07-DQB1*02-DPB1*02	Decreased antibody (two doses)	
Class II haplotype	DRB1*15/16-DQB1*06-DPB1*04	Increased antibody (two doses)	
Class I haplotype	A*26-C*12-B*38	Increased cellular (two doses)	[18]
Class II haplotype	DRB1*04-DQB1*03-DPB1*03	Increased cellular (two doses)	[18]
Class II haplotype	DRB1*03-DQB1*02-DPB1*04	Increased cellular (two doses)	

Cytokine and cytokine receptor SNP associations with humora (IgG antibody) and cellular (lymphoproliferation) immune responses to measles vaccine

Gene	SNP ID	Genotype	Phenotype
IL-2	rs2069762	GG/TG/TT	Antibody^{high} Cellular^{high}
	rs2069763	GG/TG/TT	Antibody^{high} Cellular^{high}
IL-10	rs1800890	AA/TA/TT	Antibody^{low} Cellular^{low}
	rs1800871[a]	AA/GA/GG	Antibody^{low} Cellular^{low}
	rs1800872[a]	AA/CA/CC	Antibody^{low} Cellular^{low}
IL-12RB	rs3790567	AA/GA/GG	Antibody^{low} Cellular^{low}
	rs372889	AA/AG/GG	Antibody^{low} Cellular^{low}

No. of measles vaccine doses (MMR-II)	HLA class I alleles	HLA class II alleles
1 dose	B*8, B*13, B*44	DRB1*03, DQA1*0201
2 doses	B*4403	None