Nutrition and Toxicants in Autoimmune Disease: Implications for Prevention and Treatment

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Autoimmune diseases

- “Autoimmunity” refers to a disease state in which an organism fails to recognize some aspect of “self”, resulting in an immune response against its own cells and tissues.
- At least 70-80 autoimmune diseases
- 5-8% of Americans with an AI disease; estimates vary considerably
- Systemic AI diseases: multiple body tissues affected
  - Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma,
- Organ/Tissue Specific: one tissue or organ affected
  - Hashimoto’s thyroiditis, Type I diabetes (T1D), Multiple Sclerosis (MS)

Most common AI diseases

- Rheumatoid arthritis
- Graves Disease (> over-production of thyroid hormone)
- Hashimoto's thyroiditis
- Type 1 diabetes (T1D)
- Inflammatory bowel disease (IBD)
- Multiple sclerosis
- Systemic lupus erythematosus (SLE)
- Sjögren's syndrome—damages the glands that produce tears and saliva causing dry eyes and mouth; may affect kidneys and lungs
- Systemic sclerosis (scleroderma)

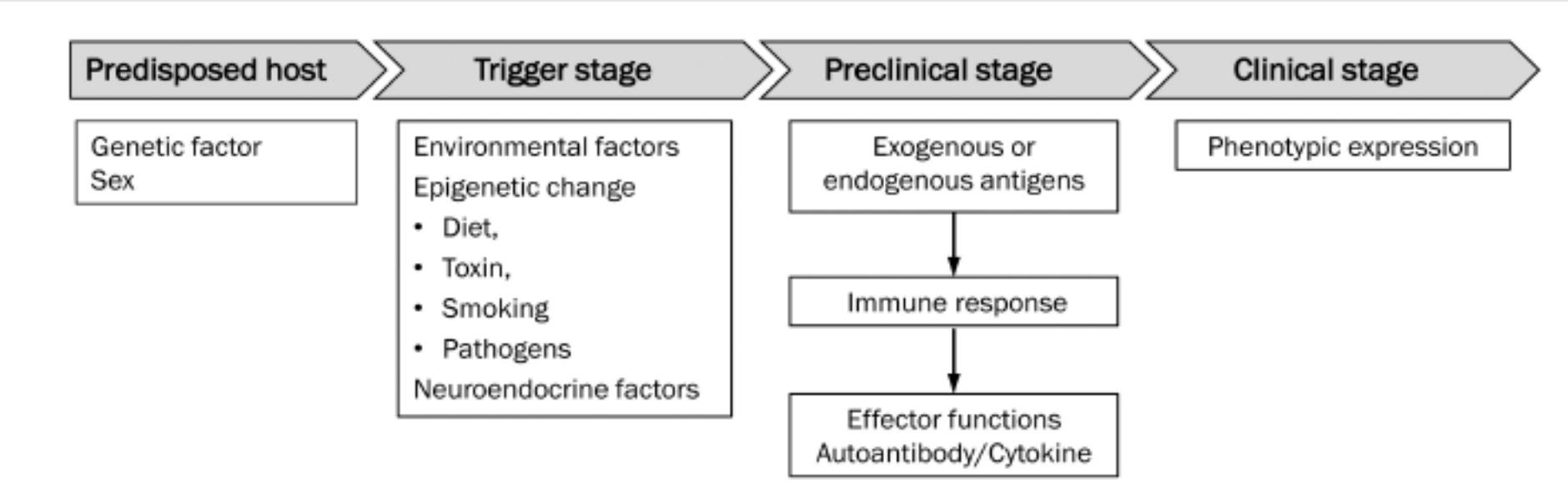
AI diseases—gender bias, trends

- Most autoimmune diseases are more prevalent in women, but a few such as T1D are equally or more common in men.
- Steady rise in AI diseases in industrialized countries over several decades (> hygiene hypothesis)
- But even among industrialized countries, there is considerable variation in specific diseases. For example, the incidence of T1D in children in Germany is slightly less than in the US and less than half of that in Sweden and Finland

Origins of AI diseases

- In general, autoimmune diseases are believed to be caused by a combination of genetic predisposition and environmental triggers.
- A number of genes have been implicated.
- But concordance rates for AI diseases in monozygotic twins are generally less than 50% and significant genetic associations are found in only a minority of patients
- This strongly supports the view that other risk factors and mechanisms are involved in the origins of autoimmunity

The importance of a life course approach



Immune system development

- Genetics
- Maternal, infant/child
  - Nutrition—micro- and macro-nutrients
  - Toxicants
  - Infections
  - Stress
  - Vaccines
- Vitamin D—inadequate levels are common; AAP recommends infant supplements; ACOG recommends testing pregnant women “at risk”
- Intestinal microbiome (influences innate and adaptive immune system)
  - Colonization begins before birth
  - Influenced by mode of delivery (C-section vs. vaginal birth)
  - Breast vs. formula feeding; other feeding practices, food introduction
  - Antibiotics
  - More general environment

Toxicants and AI disease (adults)

- Pharmaceuticals (e.g., hydralazine, procainamide—SLE-like syndrome)
- Smoking—RA, multiple sclerosis, Graves disease
- Silica (sand mining; construction; glass and pottery production)—RA, SLE, scleroderma
- Metals (mercury, silver, gold, aluminum)—AI diseases in animal models; human data are limited
- Pesticides—some but not all studies report increases in RA and SLE
- PCBs—some studies show increases in SLE, RA, anti-thyroid antibodies
- Solvents—strong evidence that occupational exposures > inc. risk of systemic sclerosis; some evidence for inc. SLE
- Estrogenic agents—some evidence for DES/MS link; BPA (plausible from animal studies but no human evidence)

Toxicants and AI disease: mechanisms

- Altered immune system development; e.g. TCDD (dioxin)
- Adjuvants: agents that stimulate the immune system without being antigens themselves; e.g. mineral oil, radiation, viruses, aluminum
- B cell activation: (antibody producing cells); through molecular mimicry or neoantigen-mediated autoantibody production—drugs; infectious agents; tobacco smoke
- Direct impairment of immune function: Altering T-cell (a whole family) production or function; the relative abundance of subtypes > major influence on the maintenance or loss of immune tolerance.
- Modifications of self-antigens
- Epigenetic changes > altered gene expression (methylation differences observed in T1D, SLE, RA, scleroderma); hypomethylated genes are “poised for expression”

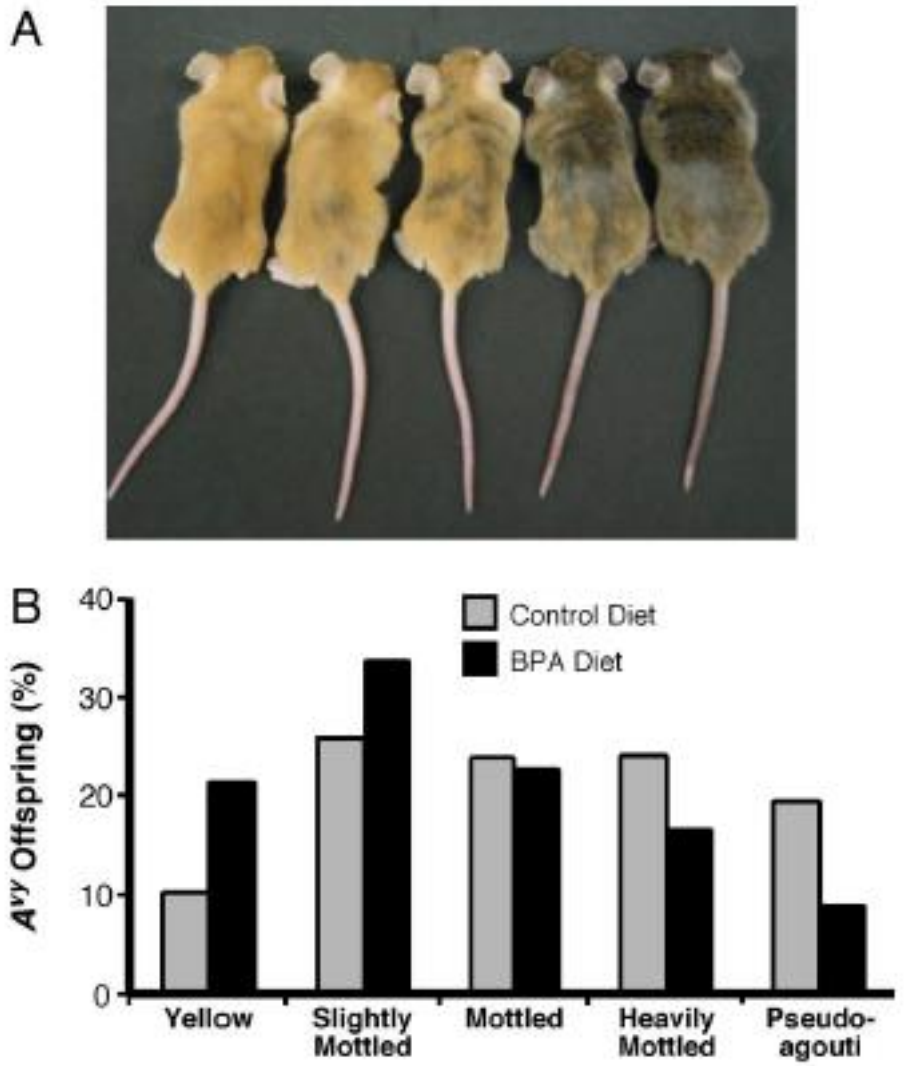


Fig. 1. Maternal BPA exposure shifts offspring coat color distribution toward yellow. (*A*) Genetically identical A^{vy}/a offspring representing the five coat color phenotypes. (*B*) Coat color distribution of A^{vy}/a offspring born to 16 control ($n = 60$) and 17 BPA-exposed ($n = 73$) litters (50-mg BPA/kg diet).

Epigenetic modifications: an example to Illustrate—not autoimmunity here

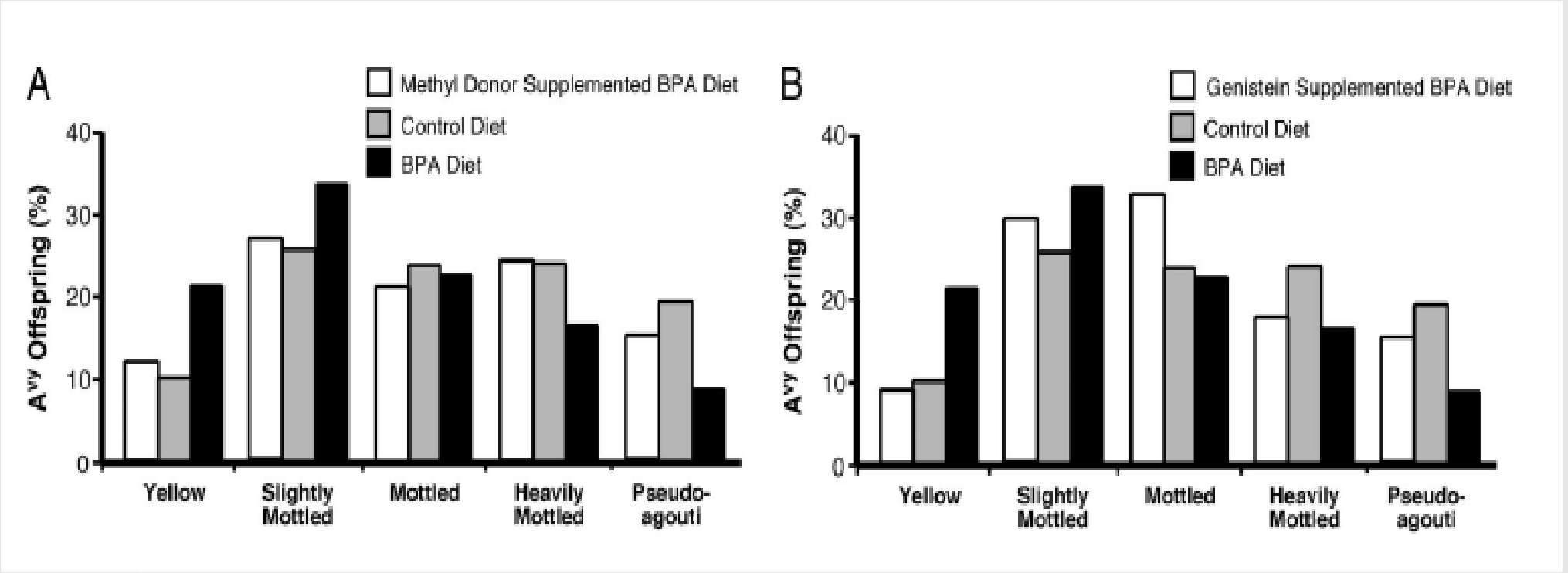
Genetically identical mice with dominant agouti alleles

Methylation influences coat color; less (hypo)methylation > yellow

Maternal BPA exposure results in DNA hypomethylation in offspring

(diabetes, obesity, and cancer also increased in the yellow mice)

Dolinoy, et al. PNAS, 2007
http://www.ncbi.nlm.nih.gov/pubmed/17670942



DNA hypomethylation can be counteracted by diet containing methyl donors (folate, B12, betaine, choline) or genistein (isoflavone in soy)

Conclusions

- The incidence of many AI diseases is increasing
- Many, multi-level, interacting variables are responsible
- Multiple mechanisms are involved
- A life course approach is essential for understanding and intervening
- An ecological (systems) framework is best suited to address this complexity
    - Recognizes the primary importance of interactions among multiple variables, across the life course
    - Accommodates efforts to re-design “system conditions” in ways that reduce risk and increase resilience; suggests places for strategic interventions
    - Helps to explain why interventions to prevent and treat AI diseases are usually not conducive to blinded clinical trials.
    - Makes clear that some amount of uncertainty will never be resolved