4. Evaluación histopatológica de tejido articular de ratones MRL/lpr infectados con bacterias o helmintos.

Todos los grupos de ratones desarrollaron artritis, (pero no así todos los ratones de cada grupo, ni desarrollaron el mismo grado de daño articular) caracterizada por inflamación y eritema, principalmente en las articulaciones de las patas posteriores (Fig 8). Todos los grupos de ratones mostraron daño articular en diferente grado (tabla IV),

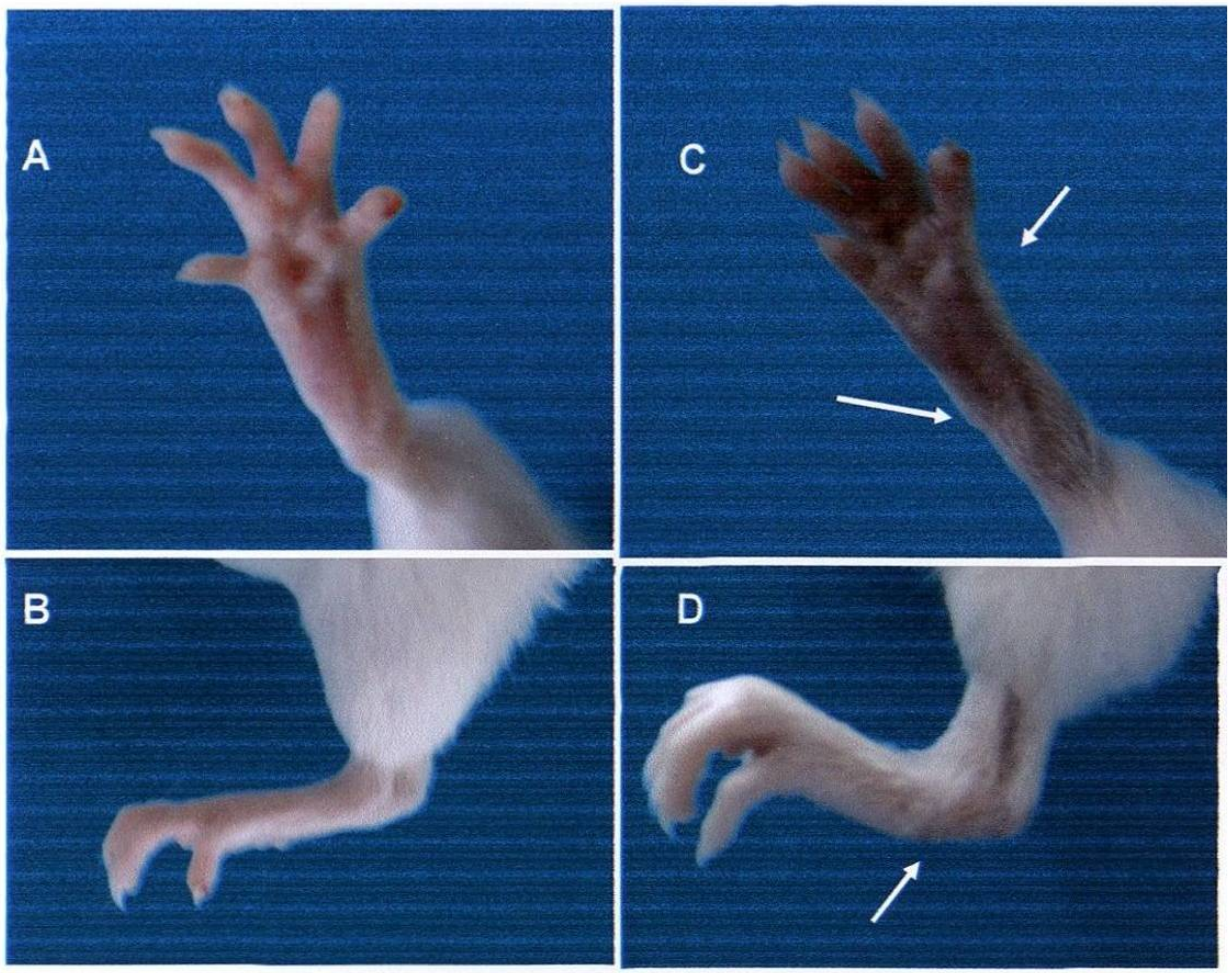
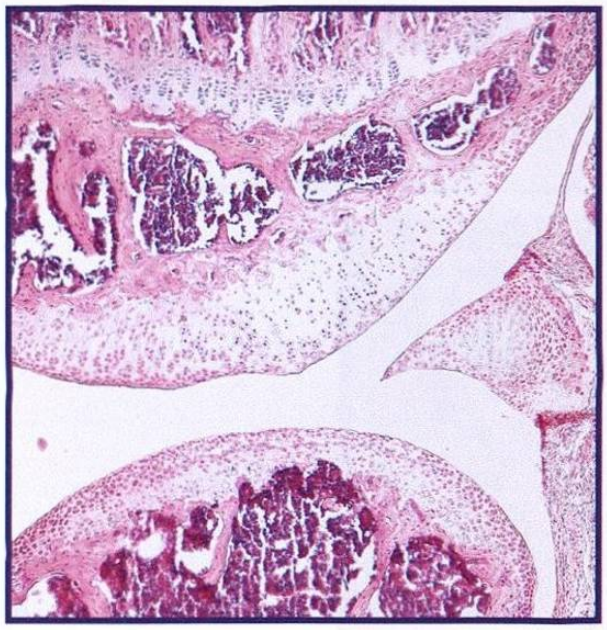
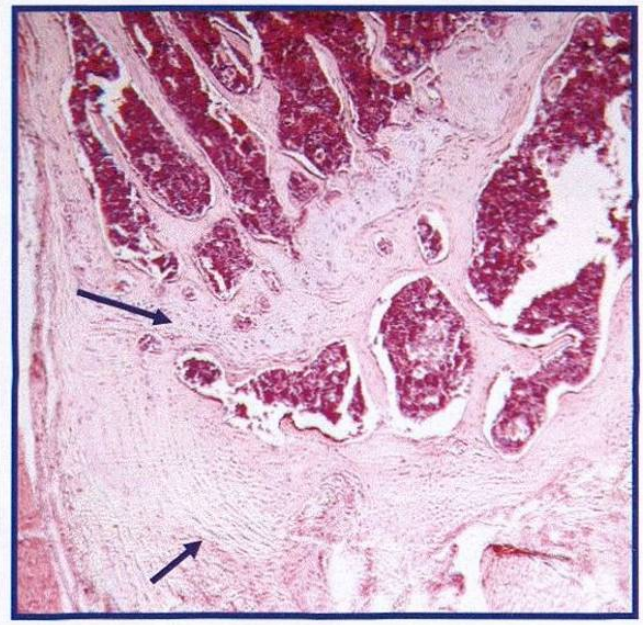


Fig 8. Evaluación clínica de la artritis en el ratón MRL/*lpr*
A y B, tren posterior de ratones control sin lesión articular
C y D, edema y eritema de pata trasera de un ratón infectado con *Staphylococcus aureus*

embargo, en algunos de los grupos hubo ratones que no desarrollaron artritis como el caso de los grupos de ratones infectados con helmintos y grupo control (Fig 8) La inflamación mas temprana ocurrió 5-6 días posteriores al tratamiento y perduró hasta el final del mismo, sin embargo algunos de los ratones de los grupos control e infectados con helmintos no desarrollaron artritis (30%). El desarrollo de artritis se evaluó por la presencia de inflamación de la sinovial, hiperplasia sinovial, pannus, erosión de cartílago o destrucción de hueso (Fig. 9).



Articulación normal



Erosión de cartílago y hueso

3. Histopatología de la articulación en el ratón MRL/*lpr*. Microfotografía de la articulación tibio-femoral en un ratón de la cepa MRL/*lpr*. A. Articulación sin daño; B. Articulación artritis. Se muestra erosión de cartílago (ec) y erosión de hueso (eh). Cortes de 5μm, tinción H y E. 10X

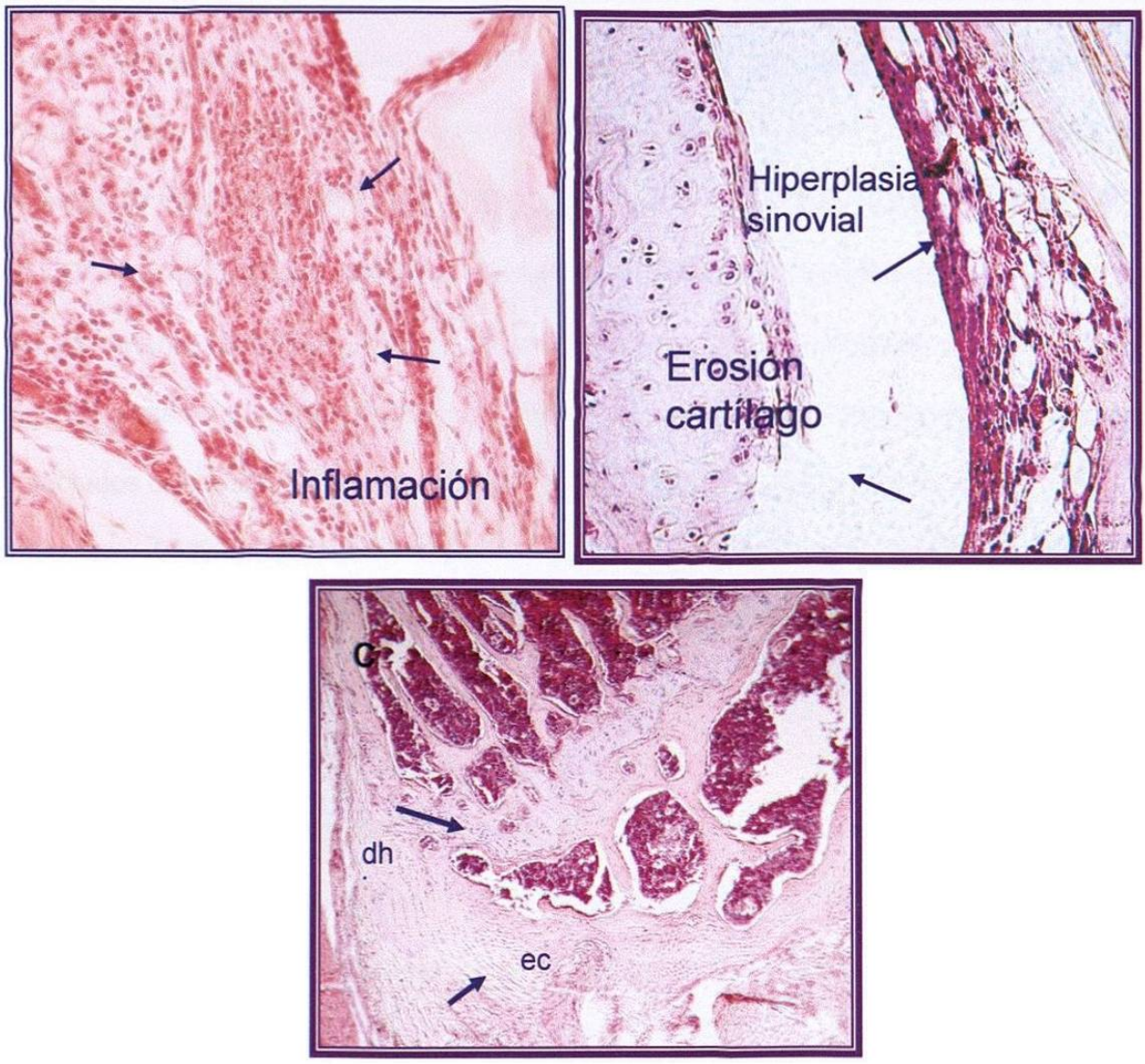


Fig 10 Microfotografía de la articulación de un ratón de la cepa MRL/*lpr* con artritis A. Inflamación de la sinovial; B. Hiperplasia sinovial con erosión d C. Erosión de cartílago (ec) y destrucción de hueso (bd). Cortes de 5μm, tinción H y E

Los grupos de ratones infectados con las bacterias *Nocardia brasiliensis*, *Staphylococcus aureus*, ly los inmunizados con ACF, incrementaron significativamente el número de ratones que desarrollaron etapas avanzadas de daño articular, tales como erosión de cartílago y hueso (P< 0.009); mientras un menor. número de ratones infectados con helmintos desarrollaron lesiones articulares severas menos, como hiperplasia sinovial, pannus y (Fig. 10) erosión de cartílago sin llegar a la etapa de destrucción de hueso incluso algunosno presentaron artritis (P< 0.042)

El 36% de los ratones MRL/*lpr* infectados *Nocardia brasiliensis* desarrollaron principalmente hiperplasia sinovial, 45% erosión de cartílago, mientras que solamente el 9% desarrollaron destrucción de hueso. Por otro lado, la mayoría de los ratones infectados con *Staphylococcus aureus* mostraron etapas avanzadas de daño articular, 30% erosión de cartílago, 60% destrucción de hueso y solamente 10% de los ratones desarrollaron pannus (10%). Una condición semejante a lo anterior fue la que se desarrolló en los ratones MRL/*lpr* inmunizados con ACF, en donde la mayoría de los ratones mostraron etapas avanzadas de la enfermedad; 50% erosión de cartílago y 30% destrucción de hueso; en cambio en los ratones control un 40% desarrollaron erosión de cartílago y 10% no desarrollo artritis. En cuanto a los grupos de ratones infectados con los helmintos *Heligmosomoides polygyrus* y *Nippostrongylus brasiliensis,* es de notar que en ambos grupos, el 30% no desarrollaron artritis, el 40% de los infectados con *Heligmosomoides polygyrus* mostró hiperplasia sinovial y el 10% destrucción de hueso; mientras que los infectados con *Nippostrongylus brasiliensis*, 40% desarrollaron erosión de cartílago y 10% erosión de hueso (Tabla 4).

Tabla IV. Las bacterias y helmintos afectan la artritis espontánea en el ratón MRL/*lpr*

Lesión tisular	AGENTE INFECCIOSO				
	Control	BACTERIA		HELMINTOS	
		N. brasiliensis	*S. aureus*	*H. p*	*Nippos*
# de ratones afectados	9/10	10/11	10/10	7/10	7/10
Inflamación sinovial	1/10	1/11	0/10	0/10	0/10
Hiperplasia sinovial	3/10	4/11	0/10	4/10	1/10
Pannus	0/10	0/11	1/10	1/10	1/10
Erosión cartílago	4/10	5/11	3/10	1/10	4/10
Destrucción hueso	1/10	1/11	6/10	1/10	1/10

El 36% de los ratones MRL/*lpr* infectados *Nocardia brasiliensis* desarrollaron principalmente hiperplasia sinovial, 45% erosión de cartílago, mientras que solamente el 9% desarrollaron destrucción de hueso. Por otro lado, la mayoría de los ratones infectados con *Staphylococcus aureus* mostraron etapas avanzadas de daño articular, 30% erosión de cartílago, 60% destrucción de hueso y solamente 10% de los ratones desarrollaron pannus (10%). Una condición semejante a lo anterior fue la que se desarrolló en los ratones MRL/*lpr* inmunizados con ACF, en donde la mayoría de los ratones mostraron etapas avanzadas de la enfermedad; 50% erosión de cartílago y 30% destrucción de hueso; en cambio en los ratones control un 40% desarrollaron erosión de cartílago y 10% no desarrollo artritis. En cuanto a los grupos de ratones infectados con los helmintos *Heligmosomoides polygyrus* y *Nippostrongylus brasiliensis,* es de notar que en ambos grupos, el 30% no desarrollaron artritis, el 40% de los infectados con *Heligmosomoides polygyrus* mostró hiperplasia sinovial y el 10% destrucción de hueso; mientras que los infectados con *Nippostrongylus brasiliensis*, 40% desarrollaron erosión de cartílago y 10% erosión de hueso (Tabla 4).

Discusión

Al infectar a un organismo, los agentes patógenos inducen una respuesta inmune tipo Th1 o Th2 al activar una subpoblación particular de LT (Del Prete, 1991; Sartono, 1996) Para evaluar el tipo de respuesta Th1 o Th2 inducida por la infección de ratones MRL/*lpr con* bacterias o helmintos, se midieron las citocinas IL-4 e IFN-γ así como las IgG1 e IgG2a. Se seleccionó IgG1 como indicador de una respuesta Th2, e IgG2a para Th1; en cuanto a las citocinas, el IFN-γ predomina en la respuesta Th1 mientras que la IL-4 es característica de Th2.

Las infecciones con helmintos se caracterizan principalmente por un incremento en el nivel de Acs IgG1 (Th2). La infección con helmintos induce una respuesta inmune que es polarizada hacia un fenotipo Th2, lo cual se refleja en la producción de citocinas, IgG1 e IgE (Lebrun, 1987; Maizels, 1993; Finkelman, 1997; Locksley, 1994; Kamata, 1995Allen, 1996; Pritchard, 1997;) así como activación de eosinófilos y células cebadas (Befus, 1979; Jarret, 1982; Finkelman, 1990). En este trabajo, los ratones infectados con los helmintos *Heligmosomoides polygyrus* o *Nippostrongylus brasiliensis* produjeron niveles significativos de Ac IgG1 en los días 21 y 42 post-infección, lo que se asocia con una respuesta Th2 y concuerda con reportes previos. Los parásitos o sus productos, como las proteasas de *Nippostrongylus brasiliensis* (Kamata, 1995) o los Ag HES y NES poseen la capacidad de inducir la síntesis de IgG1 e IgE en ratones BALB/c (Holland, 2000)

La infección de los ratones MRL/*lpr* con las bacterias *Nocardia brasiliensis* y *Staphylococcus aureus* incrementa significativamente el nivel de los Acs IgG2a (Th1). Los ratones infectados con *Staphylococcus aureus* mostraron niveles elevados de IgG2a en los días 21 y 42 post-infección, no se observaron cambios en los niveles de IgG1 como era de esperarse, ya que esta bacteria ha sido reportada

como fuerte inductora de respuesta tipo Th1. En el presente estudio se utilizó la cepa de *Staphylococcus aureus* Cowan I, cuya proteína A, es un excelente superantígeno. Esta bien documentado que contribuye a su patogenicidad e induce niveles elevados de IgG2a, característicos de una respuesta tipo Th1.

Los niveles séricos de Ac IgG2a en ratones MRL/*lpr* infectados con Nocardia se incrementaron significativamente en los días 21 y 42 post-infección, mientras que los Ac IgG1 se elevaron hasta el día 42. En el día 21 no se encontró una diferencia significativa en comparación con el control. Lo anterior evidencía la capacidad de los Ag inmunodominantes de *Nocardia brasiliensis* de generar una respuesta Th1 y Th2 durante la infección, lo que se corrobora con la determinación de niveles elevados de IgG1 e IgG2a. Resultados similares habían sido reportado en el trabajo de tesis de Pérez-Rivera (2005), al evaluar la producción de IgG en respuesta a los Ag inmunodominantes de *Nocardia brasiliensis*. En este estudio, los niveles de IgG total se elevaron de manera significativa a los 45 días post-inmunización, el Ag P24 indujo la producción de IgG1, mientras que P61 y proteasa estimularon la síntesis de IgG2b/IgG1, e IgG2a/IgG3 respectivamente.

La infección de los ratones MRL/*lpr* con helmintos induce un incremento en la síntesis de IL-4. En este trabajo, la producción sérica de IL-4 por los ratones MRL/*lpr* infectados con los helmintos *Heligmosomoides polygyrus* y *Nippostrongylus brasiliensis* fue mayor. Estos resultados concuerdan con los hallazgos reportados previamente de que la infección con los helmintos *Heligmosomoides polygyrus* y *Nippostrongylus brasiliensis,* estimulan una respuesta por células T, específicamente Th2 (Holland, 2000 Finkelman 2004).

También se observó un incremento del IFN-γ en ambos grupos de nuestros ratones infectados con helmintos, sin embargo esto se presentó en una proporción menor que

la observada en los grupos infectados con bacterias. Cabe remarcar que los ratones MRL/*lpr* tienden a presentar aun sin infección, un nivel basal de IFN-γ elevado, como se puede observar en el control (Fig 6). Lo anterior había sido previamente reportado por Takahashi (1996). Las principales citocinas en la respuesta Th2 son IL-4 e IL-13, y la presencia de IFN-γ sugiere una respuesta Th1. Clásicamente se admite que las respuestas Th1/Th2 son mutuamente excluyentes (Seder, 1994), sin embargo existe evidencia de respuesta no tan polarizada y que la infección por helmintos se acompaña de la producción de IL-4, IL-5, IL-3, pero también IFN-γ en baja concentración S (Street 1990; Svetic 1992).

Los ratones infectados con *Nocardia brasiliensis* y *Staphylococcus aureus* inducen principalmente la síntesis de IFN-γ. En este estudio, observamos que los ratones infectados con bacterias, indujeron la producción significativa de IFN-γ. Es importante señalar que el grupo de ratones infectados con *Staphylococcus aureus* indujo la mayor producción de IFN-γ. Este microorganismo promueve fuertemente una respuesta tipo Th1 y se ha reportado su capacidad para inducir la síntesis de citocinas tales como IFN-γ, TNF-α e IL-6; (Nakane, 1995). Adicionalmente, se ha descrito un incremento del IFN-γ (hasta 10 veces su nivel basal) en ratones infectados con *Nocardia brasiliensis*; aún que ésta se acompaño en los primeros días, de la producción de IL-4, IL-6 e IL-10 (Salinas-Carmona, 1999).

En este estudio, observamos que la producción de IL-4 también se elevó en ambos grupos de ratones infectados por bacterias, pero sin alcanzar el nivel del IFN-γ. Nuevamente, aunque existió un predominio de una respuesta de citocinas Th1, se observó la producción concomitante de citocinas Th2, las cuales podrían tener un papel inmunoregulador al limitar el exceso de la respuesta inflamatoria en la infección por *Staphylococcus aureus* (Sasaki 2000).

Los ratones infectados con bacterias desarrollan artritis con grados avanzados de lesión articular. De los ratones infectados con las bacterias, el 100% desarrollo artritis, con etapas avanzadas de daño articular (erosión de cartílago y destrucción de hueso). Es importante resaltar que se ocasionó artritis severa en la mayoría de los ratones. Esto podría ser explicado por la presencia del superAg en la cepa de *Staphylococcous aureus* utilizada (Bremell, 1994 y 1995).

Los ratones infectados con *Nocardia brasiliensis,* también desarrollaron daño del tejido articular y cabe la posibilidad de que las proteasas de Nocardia juegen un papel importante en estas lesiones (Vázquez 1998; Licón-Trillo, 2003). Por lo contrario, en el grupo control, el 90% desarrollo artritis, pero de ellos, solamente el 10% presentó erosión de hueso; mientras que el grupo testigo tratado con ACF presento erosión de cartílago y hueso. Este último resultado concuerda con los reportados por Ratkay (1993) y Vázquez (1998).

La infección con helmintos disminuye el número de ratones que desarrollan artritis. De los grupos de ratones MRL/*lpr* infectados con los helmintos solo el 30% no desarrollo artritis ($P< 0.042$), el 70% que si la desarrollaron, mostraron en su mayoría lesiones leves de daño articular. Este resultado fue más notable en el grupo de ratones infectados con *Heligmosomoides polygyrus* en los que 40% de los ratones desarrollaron hiperplasia sinovial sin llegar a un grado avanzado de lesión articular, solamente un 10% desarrollaron destrucción de hueso. El efecto inmunomodulador anti-inflamatorio inducido por parásitos o sus productos (huevos o proteínas) ha sido ampliamente demostrado, como es el caso de la glicoproteína ES-62 derivada de las filarias y se ha determinado que incluso es capaz de suprimir el inicio de AIC y la progresión de la artritis (Harnett: 2004).

De acuerdo a estudios recientes y a nuestros resultados, parece ser que la infección con *Heligmosomoides polygyrus* tiene la capacidad de limitar la aparición de la artritis o bien la progresión de la enfermedad en ratones MRL/lpr genéticamente predispuestos a desarrollarla.

Aunque *Nippostrongylus* disminuyó la frecuencia de aparición de la artritis, un 40% de los ratones infectados desarrollo erosión de cartílago y un 10% a la destrucción de hueso. Una posible explicación a las diferencias de respuesta entre los dos helmintos, es el tipo de enfermedad que ocasiona, mientras que la infección por *Heligmosomoides polygyrus es* crónica, en *Nippostrongylus brasiliensis* es aguda, por lo que el tiempo de contacto con los Ag difiere de un parásito a otro. La permanencia del Ag parece importante para el efecto protector.

Con el presente estudio, demostramos de una manera general, que la infección con bacterias induce una respuesta inmune tipo Th1 y acelera la artritis que desarrolla el ratón MRL/*lp*; mientras que la infección con parásitos se acompaña de una respuesta Th2 y diminuye la frecuencia de artritis. Sin embargo, no se puede generalizar y asociar estrictamente un tipo de infección (bacterias o helmintos) con un tipo de respuesta inmune (Th1, o Th2). De la misma manera, el efecto protector contra la artritis se observó claramente en el caso de *Heligmosomoides polygyrus* pero no fue así por el otro parásito. Esta diferencia de respuesta se observó también en el caso de las bacterias. Si bien *Staphylococcus aureus* al favorecer un estado inflamatorio, promueve la aparición de la artritis, la infección por *Nocardia brasiliensis* no produjo un efecto tan evidente.

Estos resultados son alentadores para investigar más ampliamente el efecto inmunomodulador de la infección por parásitos o sus productos, en el desarrollo de la artritis y su posible aplicación uso con potencial terapéutico.

CONCLUSIONES

- **La infección con *Staphylococcus aureus* induce una respuesta inmune** predominante de tipo Th1 (↑IgG2a e ↑ IFN-γ), mientras que la infección por *Nocardia brasiliensis* induce la producción de ambos tipos de Ac (IgG1 e IgG2a) y una elevación en la producción de IL-4 e IFN-γ.

- **Los helmintos *Heligmosomoides polygyrus* y *Nippostrongylus brasiliensis*,** inducen principalmente la síntesis de IgG1 y la producción significativa de IL-4, por lo que se puede inferir que provocan una respuesta de tipo Th2

- **Los helmintos *Heligmosomoides polygyrus* y *Nippostrongylus brasiliensis*,** disminuyen la frecuencia de aparición de la artritis en el ratón MRL/*lpr*. En el caso específico de *Heligmosomoides polygyrus* disminuye también el grado de daño tisular

- **En cambio, la infección de los ratones con *Staphylococcus aureus* y** *Nocardia brasiliensis*, incrementó el grado de lesión articular.

PERSPECTIVAS

- Estudiar el papel que juegan los antígenos inmunodominantes de los helmintos *Heligmosomoides polygyrus* y *Nippostrongylus brasiliensis* como agentes reguladores de una respuesta inflamatoria crónica, tal como ocurre en la artritis.

- Esto nos permitiría realizar reinmunizaciones con dichos antígenos de los helmintos, con el propósito de inducir etapas de remisión de la enfermedad, incluso implementar el desarrollo de una vacuna para el tratamiento de la artritis

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LISTA DE ABREVIATURAS

Ac	Anticuerpo
ACF	Adyuvante Completo de Freund
AcMc	Anticuerpos monoclonales
Ag	Antígeno
AIC	Artritis inducida por colágena
AR	Artritis reumatoide
BHI	Infusión cerebro corazón
% C	Porcentaje total de acrilamida-bisacrilamida en el gel
Cd	Células dendríticas
CMH	Complejo Mayor de Histocompatibilidad
CPA	Células presentadoras de Ag
ECC	Extracto celular crudo de *Nocardia brasiliensis*
FR	Factor reumatoide
H	Horas
H y E	Hematoxilina-Eosina
HES	Antígeno de excreción y secreción de *Heligmosomoides polygyrus*
HLA-B27	Antígeno de histocompatibilidad B27
IFN-γ	Interferón gamma
IL-4	Interleucina 4
LB	Linfocitos B
LES	Lupus Eritematoso Sistémico
LT	Linfocitos T
LPS	Lipopolisacárido
MØ	Macrófago
NES	Antígeno de excreción y secreción de *Nippostrongylus brasiliensis*
PAMP	Patrones moleculares asociados a patógenos
PMN	Polimorfonucleares
SDS-PAGE	Gel de poliacrilamida con dodecilsulfato de sodio
% T	Porcentaje total de bisacrilamida en el total de acrilamida
T CD4+	Linfocitos T CD4+
TCR	Receptor de la célula T
TLR´s	Receptores tipo Toll

TNF-α	Factor de necrosis tumoral alfa
Treg	Linfocitos T reguladores
UFC	Unidades formadoras de colonias