CD39/CD73/Adenosine Pathway in Progressive vs Non-progressive infections

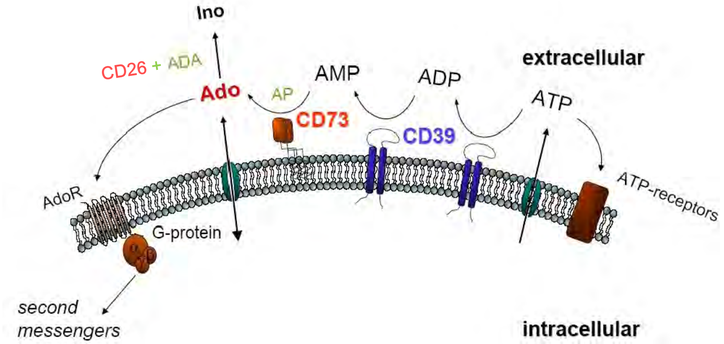
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Background

The CD39/CD73/adenosine (ADO) pathway is one of the mechanisms through which regulatory T cells (Tregs) mediate suppression of immune activation and inflammation. ADO pathway is associated with immunosuppression in multiple diseases; yet, its precise role in mediating immune activation and inflammation (IA/INFL) during HIV-1/SIV infection remains unclear.

To distinguish the role of ADO pathway in the pathogenesis of AIDS, we compared and contrasted ADO-associated markers between African green monkeys (AGMs) that control SIV-related IA/INFL and do not progress to AIDS, and pigtailed macaques (PTMs) that have aberrant IA/INFL and experience disease progression.



Methods

Infect with SIVsab

Non-Progressive Model: **AGMs** (n=5)

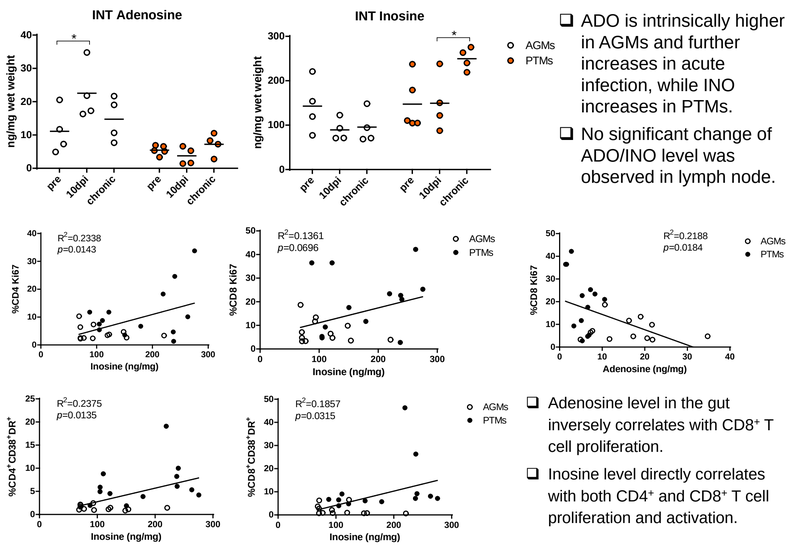
Progressive Model: **PTMs** (n=5)

ADO/INO level in tissues was measured with mass spectrometry

Correlate with immune activation and proliferation markers

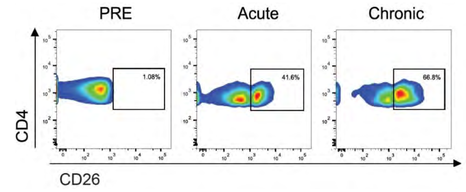
CD39/CD73 and CD26 expression is assessed by flow cytometry on T cells from blood, lymph nodes (LNs) and intestine (INT)

Adenosine/Inosine Levels in Tissues and Its Correlation with Proliferation and Immune Activation Markers

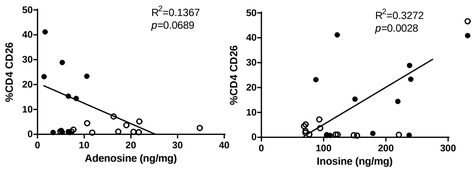


- ADO is intrinsically higher in AGMs and further increases in acute infection, while INO increases in PTMs.
- No significant change of ADO/INO level was observed in lymph node.
- Adenosine level in the gut inversely correlates with CD8⁺ T cell proliferation.
- Inosine level directly correlates with both CD4⁺ and CD8⁺ T cell proliferation and activation.

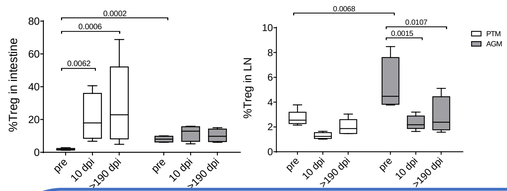
CD26 expression in PTMs vs AGMs



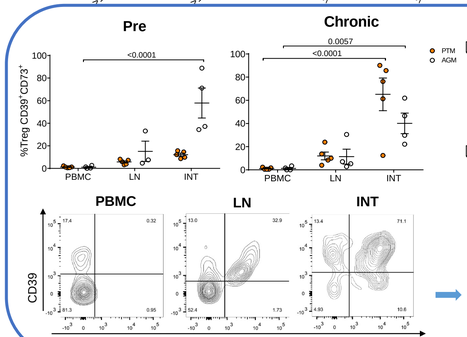
- In the intestine, CD26 expression increases dramatically in PTMs after infection, with almost 20-fold increase on CD4⁺ T cells.
- In AGMs, CD26 expression remains around pre-infection level throughout the infection.
- CD26 expression correlates with inosine level and inversely with adenosine level in the gut.



CD39 andCD73 Expression on Tregs



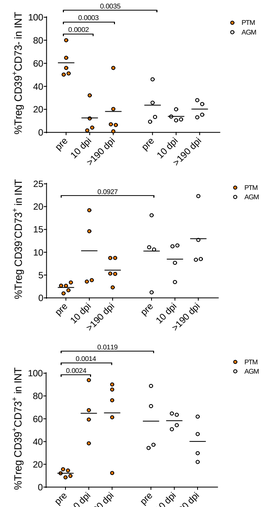
- The frequency of Tregs is intrinsically higher in AGMs in both intestine and lymph node.
- In PTMs, Tregs in intestine increased after infection, but never significantly surpassed the level in AGMs.
- No significant difference between the two species was observed in the blood throughout infection.



- The CD39/CD73 expression in the blood is similar to that in human PBMCs.
- More Tregs in intestine coexpress CD39 and CD73 than in blood, regardless of prior to or after infection.

Representative FACS plot of CD39 and CD73 expression on Tregs in AGMs prior to infection.

- CD39⁺CD73⁻ cells were intrinsically higher in PTMs but rapidly decreased after infection.
- CD39⁻CD73⁺ cells were significantly higher in the AGMs prior to infection.
- CD39⁺CD73⁺ cells were intrinsically higher in the gut in the AGMs prior to infection. An increase of the double positive cells was observed in the gut in PTMs postinfection.
- No significant change of CD39/CD73 expression on Tregs was observed in blood or LN.



Summary

- Our results strongly suggest that ADO is involved in the control of IA/INFL in nonprogressive SIV infections.
- In progressive infections ADO production appears to be counteracted by a massive increase of CD26 which occurs very early after infection.
- Changes of ADO-associated markers levels predominately occur in the gut, suggesting that future studies of the ADO pathway should focus on mucosal sites rather than in blood or LNs.

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