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501.HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

Interleukin-17A Directly Signals to Bone Marrow-Derived Hematopoietic Stem and Progenitor Cells to Promote Their Expansion and Differentiation in Vitro

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Rationale: IL-17 is a family of six pro-inflammatory cytokines (named from A to F) with distinct patterns of cellular expression. Among these, IL-17A is secreted by lymphoid subsets such as T-helper 17 cells and innate lymphoid cells type 3. Through its action on many tissues, IL-17A is recognized as a key mediator of response to infection and pathogenic states such as cancer and auto-immunity. Until now, the main effect of IL-17A on hematopoiesis has been attributed to an indirect loop through IL-17RA signaling on bone marrow stromal cells, which stimulates secretion of hematopoietic factors such as G-CSF. However, we hypothesized that IL-17A can directly signal to hematopoietic stem and progenitor cells (HSPCs) to determine their self-renewal and differentiation.
Methodology: We analyzed the expression of the IL-17 signaling pathway in publicly available human and mouse hematopoietic single-cell RNAseq datasets. Mouse HSPCs were isolated using FACS to perform clonogenic and differentiation assays in Methocult (StemCell Technologies) and StemPro-34 (Gibco). Spectral flow cytometry (SONY ID7000) was used for analysing IL-17RA expression and differentiation of mouse HSPCs. IL-17A levels were measured in blood and bone marrow serum using ELISA (Invitrogen).
Results: IL-17RA is expressed at the surface of mouse HSPCs, with greatest levels in common lymphoid progenitors and granulocyte-monocyte progenitors. mRNA expression of IL-17RA signaling pathway is also detectable in human HSPCs, with greatest levels in young individuals. IL-17A supplementation leads to an increase in clonogenic capacity of mouse HSPCs in methylcellulose colony-formation assays. In liquid culture, supplementation with IL-17A leads to a greater expansion of sorted Lin $^{-}$/s-kit $^{+}$/Sca-1 $^{+}$ progenitors, accompanied by an increased proportion of myeloid-committed cells.IL-17A is also detected in the bone marrow serum, with possible production from subsets of cells expressing RORγt, a master regulator in development of T helper 17 (Th17) cells.
Conclusions: Our work suggests the ability of IL-17A to directly promote clonogenic potential of HSPCs and drive a myeloid-biased lineage commitment in progenitor subsets. Additional studies are required to characterize the response of HSPCs to direct IL-17A signaling in vivo. Considering the important role of IL-17A as a mediator of immune response, and tissue repair, further studies are warranted to elucidate whether modulation of this pathway may be therapeutic in the context of hematopoietic failure or malignancy.

Disclosures Poon: *Strand Therapeutics:* Current Employment. **Johnson:** *Roche:* Consultancy, Honoraria; *Merck:* Consultancy, Honoraria; *Abbvie:* Consultancy; *Gilead:* Consultancy.

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