ACVR1 Expression in Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia Based on Response to Hypomethylating Agents

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INTRODUCTION

ACTIVIN RECEPTOR TYPE I (ACVR1)

- Transmembrane kinase receptor belonging to bone morphogenic protein receptors, a part of the transforming growth factor-β (TGF-β) superfamily
- Regulates hepcidin expression and consequently hematopoiesis

ACVR1 IN HEMATOLOGIC MALIGNANCIES

- ACVR1 inhibition suppresses hepcidin expression, thus restoring erythropoiesis in patients with chronic anemia, in patients with myelofibrosis
- Momelotinib (JAK1/2 and ACVR1 inhibitor) FDA-approved for intermediate- or high-risk primary or secondary myelofibrosis post-myeloproliferative neoplasm (MPN) with anemia
- ACVR1 inhibition currently being investigated in other myeloid malignancies, including lower-risk myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)
- ACVR1 expression in MDS and chronic myelomonocytic leukemia (CMML) has yet to be well-characterized

AIM

To characterize ACVR1 expression in MDS and CMML and correlate with patient characteristics and response to hypomethylating agent (HMA) therapy

METHODS

- Patients with MDS or MDS/MPN from 2008-2019
  - 74 patients with MDS
  - 38 patients with MDS/MPN, including CMML
- Baseline patient characteristics, including peripheral blood laboratory values and bone marrow data (cytogenetics, mutations) collected
- RNA sequencing on CD34+ cells performed in all samples

- Results compared to 25 healthy controls
- MDS and MDS/MPN subgroups based on World Health Organization 2016 criteria

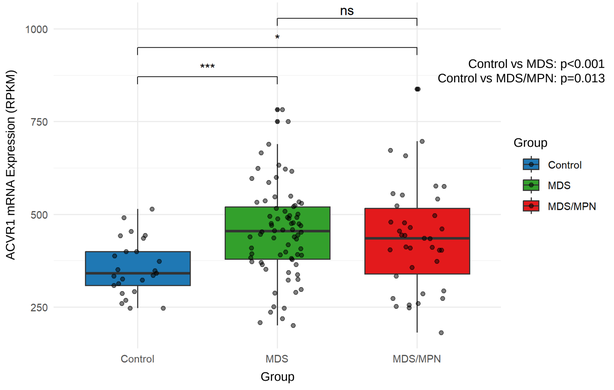
RESULTS

TABLE 1. BASELINE PATIENT CHARACTERISTICS

	n (%)/Median [Range]		
	Control N=25	MDS N=74	MDS/MPN N=38
Age [years]	24 [20-54]	70 [42-87]	73 [47-87]
Male/Female*	6 (60)/4 (40)	55 (75)/18 (25)	29 (76)/9 (24)
Laboratory Values**			
WBC [x10^9]	---	3.5 [0.6-2.1]	9.4 [2.1-67.0]
ANC [x10^9]	---	1.6 [0.20-9.4]	5.5 [0.9-41.1]
Hgb [g/dL]	---	9.4 [6.8-15.0]	10.9 [5.3-14.6]
Platelets [x10^9]	---	89 [11-331]	104 [16-707]
IPSS Risk Category***			
Low	---	14 (19)	17 (45)
Int-1	---	28 (38)	11 (29)
Int-2	---	20 (27)	6 (16)
High	---	11 (15)	4 (11)
IPSS-R Risk Category***			
Very Low	---	3 (4)	4 (11)
Low	---	18 (25)	17 (45)
Intermediate	---	16 (22)	6 (16)
High	---	14 (19)	7 (18)
Very High	---	22 (30)	4 (11)

*unknown in 15 controls and 1 MDS patient
**1 MDS patient missing labs
***IPSS and IPSS-R missing in 1 MDS patient

FIGURE 1. ACVR1 EXPRESSION IN MDS, MDS/MPN, AND CONTROL COHORTS



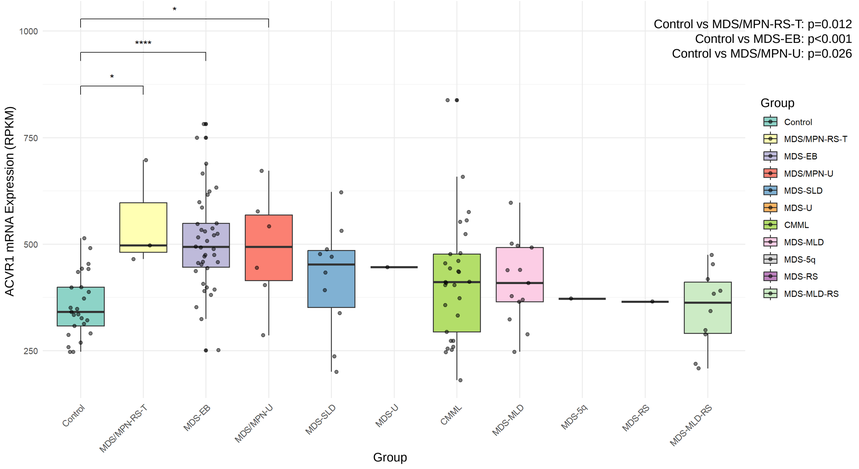
CORRELATION WITH RESPONSE TO HMA THERAPY

56 MDS and 20 MDS/MPN patients received HMA

No difference in ACVR1 expression levels for MDS patients based on HMA response (p=0.979)

MDS/MPN non-responders trended toward higher ACVR1 expression levels (p=0.095)

FIGURE 2. ACVR1 EXPRESSION IN WHO 2016 DISEASE SUBGROUPS VS CONTROL COHORT



WHO 2016 CRITERIA

MDS: N=74

- MDS-EB: n=38 (51%)
- MDS-MLD: n=13 (18%)
- MDS-SLD: n=10 (14%)
- MDS-MLD-RS: n=10 (14%)
- Other: n=3 (4%)

MDS/MPN: N=38

- CMML: n=29 (76%)
- MDS/MPN-U: n=6 (16%)
- MDS/MPN-RS-T: n=3 (8%)

CORRELATION WITH ANEMIA

No correlation observed between ACVR1 expression levels and baseline hemoglobin (ρ= -0.062, p=0.519)

CONCLUSIONS

- ACVR1 is upregulated in patients with MDS-EB, MDS/MPN-U, and MDS/MPN-RS-T
- Increased ACVR1 expression may also be associated with HMA non-responders
- Further investigation into ACVR1 as a potential therapeutic target in MDS and MDS/MPN is warranted

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