Chemokine receptor 2 (CCR2) mediates mechanical and cold hypersensitivity in chronic sickle cell disease pain

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Pain in sickle cell disease (SCD)

To what extent do peripheral inflammatory mediators contribute to sickle cell disease hypersensitivities?
CCL2 elevated in SCD patients and mouse models

Modified from Quari et al. (2012)
One-way ANOVA: main effect of group (p<0.05)
Tukey post-test: **p<0.01

Unpaired t-test: *p<0.05
CCR2 signaling mediates cold behavioral sensitivity

**CCR4 antagonist**

- Vehicle
- C-021

- B6;129: 6, 6
- Berk SS: 5, 6

**CCR2 antagonist**

- Vehicle
- RS-504393

- B6;129: 5, 6
- Berk SS: 5, 5

3 mg/kg, s.c.  
Two-way ANOVA: effect of genotype (p<0.05)  
Bonferroni post-test: # p<0.05, ### p<0.001
Assessing contributions of CCR2 to sensory neuron cold sensitivity

![Graph showing changes in F/F (%) over time for Vehicle or RS 504393.](image)
CCR2 does not appear to mediate sensory neuron cold sensitivity

10 μM RS 504393
Two-way ANOVA: effect of genotype (p<0.05)
Bonferroni post-test: # p<0.05, ## p<0.01
CCR2 signaling mediates mechanical behavioral sensitivity

CCR4 antagonist

3 mg/kg s.c.
Two-way ANOVA: effect of genotype (p<0.05)

Vehicle
C-021

Withdrawal threshold (mN)

B6;129
Berk SS
8 8
8 8

CCR2 antagonist

3 mg/kg s.c.
Two-way ANOVA: effect of drug (p<0.05), genotype (p<0.05)
Bonferroni post-test: ##p<0.01

Vehicle
RS 50439 3

Withdrawal threshold (mN)

Berk AA
Berk SS
6 6
10 10

TRPV1 antagonist

10mg/kg i.p.
Two-way ANOVA: effect of interaction (p<0.05), genotype (p<0.05);

Vehicle
Abt-102

Withdrawal threshold (mN)

B6;129
Berk SS
7 12
8 13

Adapted from Hillery et al (2011) Blood
TRPV1 is sensitized in Berk SS neurons

Two-way ANOVA: effect of capsaicin concentration (p<0.05), genotype (p<0.05)
Bonferroni post-test: ## p<0.01, ### p<0.001
TRPV1 neuronal sensitization is mediated by CCR2

5 nM capsaicin + 10 μM CCR2 antagonist

5 nM capsaicin + 100 nM CCL2

Two-way ANOVA: effect of genotype (p<0.05)
Bonferroni post-test: ### p<0.001
CCR2 Signaling Mediates:

- Cold behavior sensitivity
- Mechanical behavior and neuronal sensitivity (TRPV1-dependent)

Future direction: CCR2/TRPV1 coupling mechanism