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Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterized by joint destruction and severe morbidity. Methotrexate (MTX) is the standard first-line therapy of RA. However, about 40% of RA patients are unresponsive to MTX treatment. Regulatory T cells (Tregs, CD4(+)CD25(+)FoxP3(+)) are thought to play an important role in attenuating RA. To investigate the role of Tregs in MTX resistance, we recruited 122 RA patients (53 responsive, R-MTX; 69 unresponsive, UR-MTX) and 33 healthy controls. Three months after MTX treatment, R-MTX but not UR-MTX showed higher frequency of peripheral blood CD39(+)CD4(+)CD25(+)FoxP3(+) Tregs than the healthy controls. Tregs produce adenosine (ADO) through ATP degradation by sequential actions of two cell surface ectonucleotidases: CD39 and CD73. Tregs from UR-MTX expressed a lower density of CD39, produced less ADO, and had reduced suppressive activity than Tregs from R-MTX. In a prospective study, before MTX treatment, UR-MTX expressed a lower density of CD39 on Tregs than those of R-MTX or control ($P < 0.01$). In a murine model of arthritis, CD39 blockade reversed the antiarthritic effects of MTX treatment. Our results demonstrate that MTX unresponsiveness in RA is associated with low expression of CD39 on Tregs and the decreased suppressive activity of these cells through reduced ADO production. Our findings thus provide hitherto unrecognized mechanism of immune regulation in RA and on mode of action of MTX. Furthermore, our data suggest that low expression of CD39 on Tregs could be a noninvasive biomarker for identifying MTX-resistant RA patients.