Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions.

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The endogenous cellular and molecular mechanisms that control acute inflammation and its resolution are of wide interest. Using self-resolving inflammatory exudates and lipidomics, we have identified a new pathway involving biosynthesis of potent antiinflammatory and proresolving mediators from the essential fatty acid docosahexaenoic acid (DHA) by macrophages (MPhis). During the resolution of mouse peritonitis, exudates accumulated both 17-hydroxydocosahexaenoic acid, a known marker of 17S-D series resolvin (Rv) and protectin biosynthesis, and 14S-hydroxydocosa-4Z,7Z,10Z,12E,16Z,19Z-hexaenoic acid from endogenous DHA. Addition of either DHA or 14S-hydroperoxydocosa-4Z,7Z,10Z,12E,16Z,19Z-hexaenoic acid to activated MPhis converted these substrates to novel dihydroxy-containing products that possessed potent antiinflammatory and proresolving activity with a potency similar to resolvin E1, 5S,12R,18R-trihydroxyeicosa-6Z,8E,10E,14Z,16E-pentaenoic acid, and protectin D1, 10R,17S-dihydroxydocosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid. Stable isotope incorporation, intermediate trapping, and characterization of physical and biological properties of the products demonstrated a novel 14-lipoxygenase pathway, generating bioactive 7,14-dihydroxydocosa-4Z,8,10,12,16Z,19Z-hexaenoic acid, coined MPhi mediator in resolving inflammation (maresin), which enhances resolution. These findings suggest that maresins and this new metabolome may be involved in some of the beneficial actions of DHA and MPhis in tissue homeostasis, inflammation resolution, wound healing, and host defense.