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## **Biochemical implication of halide anions**

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Halide ions occur abundantly in Nature and are often associated with vital chemical and biochemical processes (Suzukia *et al.*, 2006; Stolting *et al.*, 2014). Among the halides, bioavailability of  $F^-$  anion (1.3 ppm) is lower in sea water relative to  $Cl^-$  anion (20,000 ppm) and  $Br^-$  anion (70 ppm). Even the least abundant halide ion, i.e.  $I^-$  anion (0.02 ppm in surface water), had been found in ~ 120 iodine-containing natural products as it is easily oxidized by haloperoxidases to iodonium ion ( $I^+$ ) (Kazuaki, 1997; Pee and Curr, 2012; Vaillancourt *et al.*, 2006).

$F^-$  anion is the 13<sup>th</sup> most abundant element in Earth's crust, mostly found in ground water.  $F^-$  anion has the highest enthalpy (~120 kcal/mole), which creates problem in nucleophilic catalysis from water, as the enzyme has to evolve a desolvation strategy (Furuya *et al.*, 2011). The haloperoxidases are unable to oxidize  $F^-$  anion because the oxidation potential of hydrogen peroxide (-1.8 eV) is lower than that of  $F^-$  (-2.87 eV) but higher than that of the other halogens ( $Cl^- = -1.36$  eV;  $Br^- = -1.07$  eV;  $I^- = -0.54$  eV) (Ballschmiter, 2003). These anomalous physical properties of  $F^-$  anion have limited the evolution of fluorine biochemistry and only 21 biosynthesized fluorine containing natural molecules are

known, compared to thousands of chlorine and bromine containing homologues.

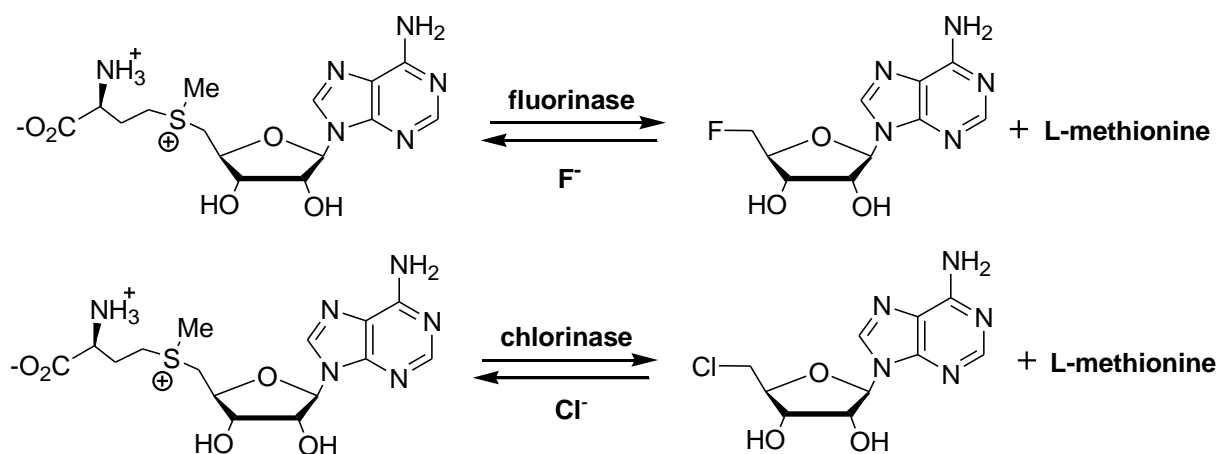
Large diversity of halogenated compounds has been found in the environment. Different halogenating enzymes like *haloperoxidases*, *halogenases*, etc. play a major role in biocatalytic incorporation of halogen into natural products and biomolecules (Perrin, 2007). *Haloperoxidases* such as *chloroperoxidases* catalyse the halogenation reaction, where they may directly involve halide anions ( $Cl^-$ ,  $Br^-$  or  $I^-$  but not  $F^-$ ) or chlorite ( $ClO_2^-$ ) or hypohalous acid (HOX) as halogenating agents (Van pee, 2003; Hofrichter and Ullrich, 2006; Muffler *et al.* 2007). They differ by the cations present in the prosthetic group which mostly contain heme iron or vanadate co-factor (Vaillancourt *et al.*, 2006).

Interestingly, halogenases like  $\alpha$ -KG-dependent halogenases and flavin dependent halogenases are capable of catalysing the regioselective carbon-halogen bond formation (Hasegawa *et al.*, 1999; Keller *et al.*, 2000; Hagan *et al.*, 2002).

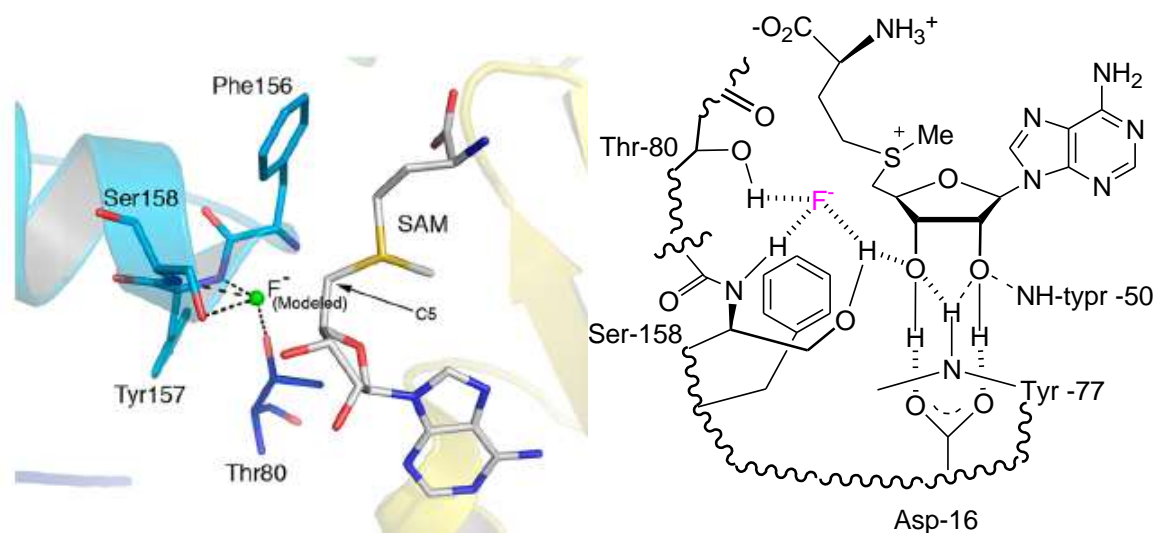
The fluorinating enzyme was first isolated from the soil bacterium *Streptomyces cattelya* and subsequently three more fluorinating enzymes had been identified

(Sanada *et al.*, 1986; Deng *et al.*, 2002; Huang *et al.*, 2014). When the bacterium grows in a medium containing  $F^-$  anion, the secondary metabolism produce bioactive fluorinated natural products (Schaffrath *et al.*, 2003). For instance, it was showed that fluorinase catalyzed the nucleophilic substitution reaction

of 5'-carbon of the ribose ring of S-adenosyl-L-methionine (SAM) involving  $S_N2$  pathway (Scheme 1) to generate 5'-fluorodeoxyadenosine (5'-FDA) and L-methionine (Flury and Papritz, 1993; Schaffrath *et al.*, 2003; Deng *et al.*, 2014).



**Scheme 1:** Reactions of the fluorinase and the chlorinase, catalysing nucleophilic attack to C-5 of SAM but with different nucleophiles (Deng *et al.*, 2014).



**Figure 1:** Structure of the active site of fluorinase showing the binding of  $F^-$  and SAM prior to the displacement reaction: (a) crystal structure, (b) model structure.

$Cl^-$  ion is essential to human health and is transported across cell membranes by various proteins. It maintains osmotic pressure and pH across cell membrane and helps in

restoration of normal acid-base and potassium equilibrium. Numerous applications in industry ranging from anti-freezing agents to metal processing require the use of halide ions.

Although occur naturally, F<sup>-</sup> and Br<sup>-</sup> anions may be environmental pollutants, both of them being toxic at high concentration (Chiun, 1996; Vengosh and Pankratov, 1998; Ayoob and Gupta, 2006; Peckham and Awofeso, 2014). Br<sup>-</sup> anion is an undesired by-side product of a number of industrial chemical processes (Aumont and Tressol, 1986; Haldimann *et al.*, 1998). It is used as a sedative and anticonvulsant in medicine and in photographic industry. I<sup>-</sup> anion is involved in thyroid physiology, photo electrochemical solar cells and as a cofactor in many antimicrobial actions (Jalali *et al.*, 2005).

Previous studies suggested that low levels of F<sup>-</sup> anion can benefit dental health and can widely be used for the prevention of dental

caries, in treatment of osteoporosis and water purification (Kleerekoper, 1998; Loe, 2000). It is present in many products associated with oral hygiene and in a number of minerals (Kissa, 1997; Geddes, 2001). However, excessive ingestion may result in fluorosis, nephrotoxic changes, urolithiasis and even kidney disorders (Harper and Hagan, 1994; Cittanova, 1996; Siener and Hesse, 2003; Deng *et al.*, 2004).

#### Conclusion:

The halide anions are very much essential in our day to day life from environmental, biological and chemical points of view. They play a significant role in several biochemical reactions. Thereby it's important to study these anions and their utility.

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