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Introduction:

Chondrocalcinosis is the calcification of cartilage seen in many diseases (e.g. hypophosphatasia, Wilson disease, and hemochromatosis); when caused by the deposition of calcium pyrophosphate (CPP) dihydrate crystals the specific term CPPD is used. CPPD has a poorly understood pathophysiology, but a simple explanation is that CPPD is caused by an excess of extracellular pyrophosphate (PPi) bound to calcium that is deposited into the cartilage of joints. A better understanding of this disease's mechanism could lead to targeted treatment. In cases of autosomal dominant CPPD, mutations in the gene coding for ANKH have been observed. ANKH is proposed to function as a transporter of PPi; however, recent reports demonstrate that ANKH may also perform other functions. The purpose of this literature review is to evaluate our current understanding of ANKH function in an effort to propose future lines of research that could target ANKH in CPP-containing diseases.

Methods:

Review was done using PubMed. Google Scholar did show other papers that did not come up in the PubMed search, but those papers were referenced in reviews that did show in the PubMed search.

- Search terms included ANKH (where "H" infers human) and ANK – the original abbreviation for the progressive ankylosis gene in a mouse model. Recovered publications that included the term ANK in referring to the ankyrin family of proteins, as well as ankh, referring to the Egyptian amulet, were excluded.

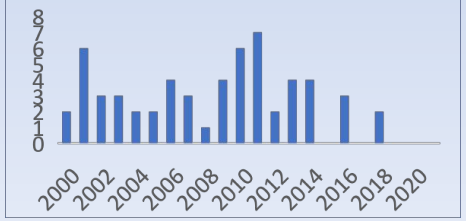
Results:

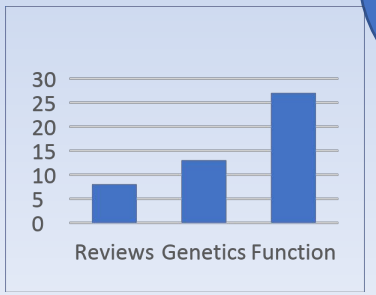
Between 2000 and 2019, a total of 58 publications have explored the genetics and function of ANKH/ANK. The yearly number distribution of papers is shown in Figure 1A. The distribution of subject matter with respect to ANKH is shown in Figure 1B.

Most notable reports:

- ANKH has been shown to interact with other proteins in the development of CPPD.
- Several diseases with evidence of calcification derangement are not linked to defects in ANKH, including ankylosing spondylitis
- ANKH may also regulate ATP transport, and its expression is sensitive to oxygen
- **Most recently: ANKH appears to play a critical intracellular role in endosomal recycling (Ref 3).**

Figure 1A



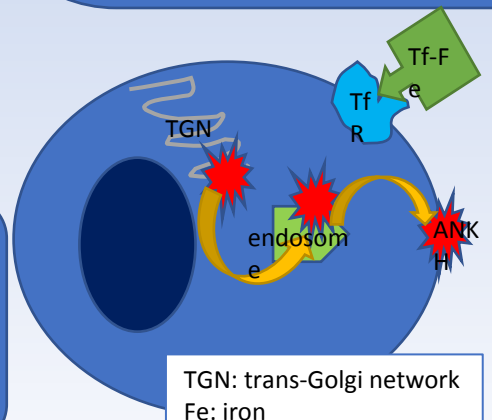


References:

1. Mitton-Fitzgerald E, Gohr CM, Bettendorf B, Rosenthal AK. The Role of ANK in Calcium Pyrophosphate Deposition Disease. Curr. Rheumatol Rep. 2016;18(5). doi:10.1007/s11926-016-0574-z. Review
2. Williams CJ. The role of ANKH in pathologic mineralization of cartilage. Curr. Op. Rheumatol. 2016;28(2):145-151. doi:10.1097/bor.0000000000000247. Review
3. SeifertW, Posor Y, Schu P, Stenbeck G, Mundlos S, Klaassen S, Nurnberg P, Haucke V, Kornak U, Kuhnisch J. The progressive ankyloses protein ANK facilitates Clathrin- and adaptor-mediated membrane traffic at the trans-Golgi network-to-endosome interface. Hum Molec Genet. 2016; 25(17):3836-3848. doi:10.1093/hmg/ddw230.

Discussion:

Mutation in the ANKH gene was first described in 2000 in a phenotype of progressive ankylosis in a naturally-occurring mouse model of abnormal mineralization. At that time, the ANKH transmembrane protein was proposed to act as a putative transporter for PPi. However, an exciting new role for ANKH was reported in 2016 with the discovery that loss of ANKH results in perinuclear accumulation of early endosomes and reduced transferrin receptor/transferrin (TfR/Tf) endocytosis (Ref 3). Hereditary hemochromatosis (HH) is caused by mutations in the HFE gene and is characterized by increased cellular uptake of iron via TfR/Tf endocytosis. Interestingly, >30% of patients with hemochromatosis suffer from CPPD. We hypothesize that iron overload may increase ANKH expression and potentiate increased generation of PPi. Experiments designed to explore ANKH expression and function in response to iron overload in HH patients would provide evidence for the role of ANKH in PPi metabolism and subsequent CPP deposition in HH patients. Furthermore, such studies would provide a rationale for the pharmacologic targeting of ANKH expression and function in HH-CPPD sufferers.



TGN: trans-Golgi network
Fe: iron

Proposed role for ANKH in the endocytosis of Tf. Seifert et al (3) show that loss of ANKH results in reduced Tf endocytosis. We hypothesize that in HH patients, increased intracellular Fe increases ANKH expression, thus resulting in increased PPi generation and ensuing CPP deposition.