Non-freezing cold injury is a persistent medical problem in a military context. This is the reason for FFI’s research on molecular responses to cold stress.

Non-freezing cold injury

Cells respond to stressful stimuli by activation of defence reactions. At FFI we investigate such defence reactions in cells from human skin after exposure to +5 °C. Insight into cellular defence reactions may lead to novel treatment strategies against cold injury.

Trench foot
Trench foot, or non-freezing cold injury, is well known from military history, and it remains a significant medical problem in operations in a cold and wet environment even during summer. Preventive measures, such as keeping extremities warm, dry and in motion, and frequent changes into dry clothing, have proven difficult under field conditions. Cold injury may be incapacitating, and it may cause persistent pain and hypersensitivity to cold. Cells of the nervous system, musculature, blood vessels, and skin may be affected during cold injury. At present no pharmacological intervention is available to counteract development of cold injury.

Molecular responses to cold injury
Cells activate multiple intracellular pathways to be able to resist and repair cell damage due to pathological environmental stress. Such stress may, however, also lead to death of the cell through genetically programmed processes. The purpose of genetically programmed cell death is to
avoid secondary damage to the tissue that surrounds the damaged cells. Insights gained from studies of cell responses to stress may lead to new therapeutic approaches to reduce the harmful effects of stress on cells.

**Cold stress**
Various intracellular pathways of relevance to cold stress are studied at FFI:
- Protein kinase cascades
- Stress protein response
- Proinflammatory stress response.

We have shown that warming cold exposed cells to 37 °C causes rapid activation of protein kinase cascades and stress protein responses. Specifically, enzymes and small stress protein become phosphorylated, and protective stress proteins are produced in the cells.

**Interventions**
Our results suggest possible interventions to reduce cold injury; pre-conditioning and antioxidants.

Tolerance to cold injury would be enhanced if protective stress proteins were formed in advance of cold exposure (pre-conditioning 2-4 hrs before) and if antioxidants were administered before warming of cold tissue.

The interventions may be effective for various cell types, since the molecular stress responses are common to all cells. Interestingly, high levels of phosphorylated small stress proteins have been shown to improve survival of both sensory and motor nerves after exposure to stressors other than low temperature.

**Cold injury**
Due to circumstances of combat, many British casualties of non-freezing cold injury in the Falkland War 1982 were Royal Mariners who were well equipped and trained for arctic conditions.

**Initial symptoms** of cold injury (during cold exposure): Colour change to pale white feet (or hands) due to intense constriction of blood vessels, numbness and other sensory disturbances.

**Later symptoms** of cold injury (following cold exposure): Swelling, edema, and colour change from pale blue skin to redness followed by intense pain.

**Predisposing factors** are:
Dehydration, tight clothing, fatigue and malnutrition.

**Early stage of non-freezing cold injury.** Cold-injured feet must be dry and warm before the soldier continues military operations. Cold injury may occur in a wet environment even in summer. (Photo: Per Kristian Opstad, FFI)