Development of an adverse outcome pathway for deposition of energy leading to bone loss.

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Abstract

Bone loss, commonly seen in osteoporosis, is a condition that entails a progressive decline of bone mineral density and microarchitecture, often seen in post-menopausal women. Bone loss has been widely reported in astronauts exposed to a plethora of stressors and in patients with osteoporosis following radiotherapy for cancer. Studies on mechanisms are well documented but the causal connectivity of events to bone loss development remains incompletely understood. Herein, the adverse outcome pathway (AOP) framework was used to organize data and develop a qualitative AOP beginning from deposition of energy (the molecular initiating event) to bone loss (the adverse outcome). A literature review was conducted to compile and evaluate the state of knowledge based on the modified Bradford Hill criteria. Following review of 1865 studies, an empirically supported AOP was developed, showing the progression to bone loss through many factors affecting the activities of bone-forming osteoblasts and bone-resorbing osteoclasts. The structural, functional, and quantitative basis of each proposed relationship was defined, for inference of causal changes between key events. Current knowledge and its gaps relating to dose-, time- and incidence-concordance across the key events were identified, as well as modulating factors that influence linkages. The new priorities for research informed by the AOP highlight areas for improvement to enable development of a quantitative AOP used to support risk assessment strategies for space travel or cancer radiotherapy.

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Figure 4: Summary of the Bradford Hill criteria (plausibility, incidence concordance, dose concordance, time concordance, essentiality, upward panel) and the stressor types supporting the AOP (lower panel). The level of evidence for each evidence stream and the percent of studies using each stressor to support the AOP were determined. Not all stressors support each KER; details can be found in the AOP Wiki.

Figure 5: Summary of the domain of applicability and doses used in the AOP. Studies were grouped by life stage (animal studies only), taxonomic, and radiation dose. Animal life stage is defined in Soergel et al., 2014 for rats, in Davis & Soergel, 2016 for rabbits, and in Linley et al., 2014 for mice. Not all dose ranges support each KER; details can be found in the AOP Wiki. Under taxonomic applicability, “other” refers to bovines, guinea pigs, piglets, rabbit, squirrel, and monkey. *Studies derived from in vitro models do not specify life stage.

Figure 6: Summary of findings. Visual representation of evidence supporting the AOP (LEOPred), stratified based on evidence stream, taxonomic applicability, linear energy transfer (LET), and dose range. The AOP is predominantly supported by ionizing radiation stressors and the breakdown of the doses is as follows: low doses were defined as ≤ 0.1 Gy, moderate doses were in the range of 0.1–1 Gy, and high doses were > 1 Gy. High LET radiation includes neutrons and heavy ions, and low LET radiation includes protons, X-rays, and gamma rays. Not all stressors and dose ranges support each KER in the AOP; details can be found in the AOP Wiki. The size of each boxed section is representative of the relative number of articles supporting that category.
Figure 7. Systematic evidence map depicting the quantity of evidence supporting each key event relationship (KER). Key events (KEs) are represented as circles, and KERs are arrows. The size of each arrow represents the weight of evidence as determined by the number of articles supporting the relationship in the form of biological plausibility, empirical evidence and essentiality studies. Articles could be used to support multiple KERs.

Supplementary: Figure 1. PRISMA diagram depicting reference screening during the coping review as described in Kothapudi et al. 2021. “Other sources” refers to papers retrieved outside of literature searches (e.g., from subject matter experts and references included of review articles). “Collection of evidence for AOP building” includes papers from other AOPs that share one or more KERs with this AOP. References could be excluded for multiple exclusion reasons (Page 6).

Selected referencesEndnote 7 (Page 12)