THERAPEUTIC EFFECTS OF METFORMIN ON NITROGEN MUSTARD–INDUCED SKIN INJURY IN A PERFUSED HUMAN SKIN MODEL

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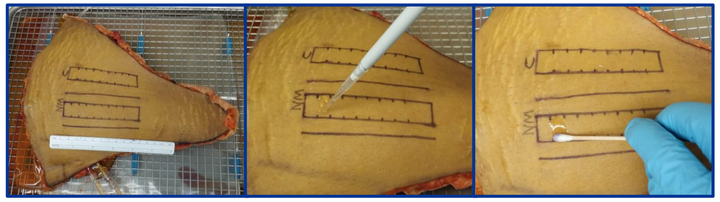
INTRODUCTION

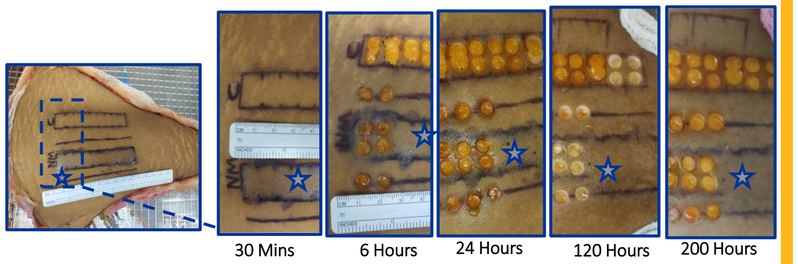
Nitrogen mustard (NM), a potent vesicant and alkylating agent, causes severe skin injury marked by inflammation, immune cell infiltration, and structural degradation. Despite its known toxic effects, the progression of inflammation and tissue remodeling in human skin remains incompletely characterized. This study utilizes an ex vivo human skin perfusion model to investigate NM-induced damage and evaluate the therapeutic efficacy of metformin, an anti-inflammatory and tissue-protective compound.

MATERIALS & METHODS

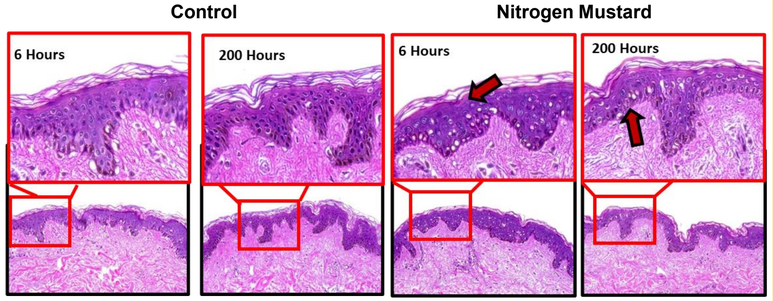
Full-thickness human skin flaps were perfused and exposed to NM at 10, 30, and 60 mg/cm².



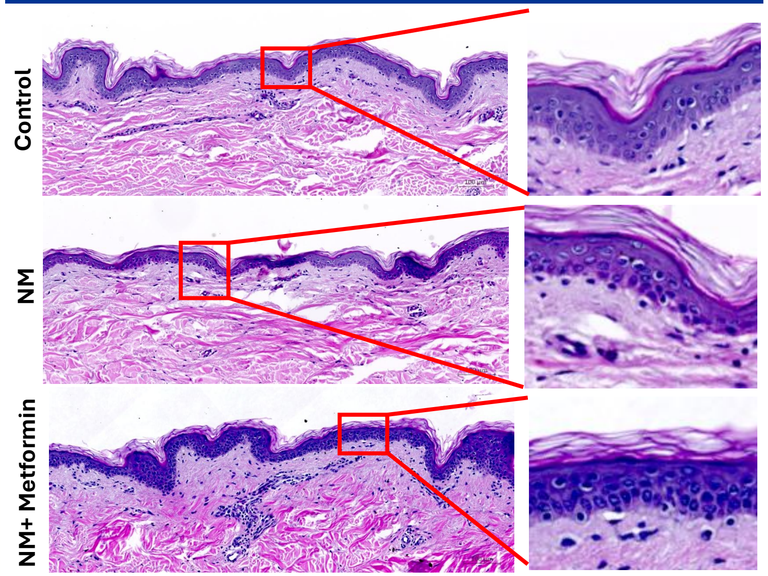
A subset received 10% metformin treatment post-exposure. Controls included untreated, vehicle (acetone:PBS), and NM-only groups. Biopsies were collected at 0, 2, 6, 24, 125, 200, and 250 hours. Histological analysis via Hematoxylin and Eosin (H&E) staining assessed tissue architecture and immune infiltration. TUNEL assay quantified cell death and HMGB1 immunostaining assessed damage-associated molecular signaling.

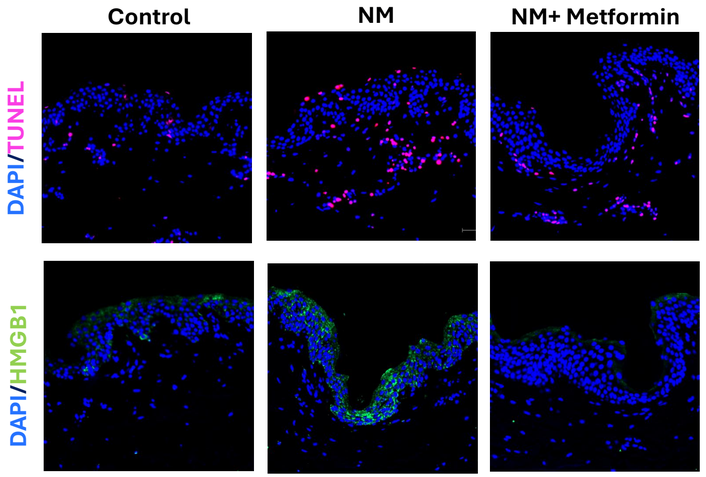


RESULTS



NM caused dose-dependent epidermal thinning, dermal separation, and inflammation. H&E staining showed nuclear vacuolization and ballooning degeneration, especially at higher NM doses





Metformin reduced NM-induced inflammation and helped preserve epidermal and dermal structure.

At 2–6 h: NM caused acute dermal inflammation; metformin lowered cellular infiltration.

At 24 h: Immune cell infiltration increased with NM dose; metformin significantly reduced infiltration.

TUNEL staining showed increased apoptosis and HMGB1 was upregulated after NM exposure, both of which were reduced with metformin.

At 200–250 h: Metformin-treated skin displayed greater recovery and restored structural integrity compared to NM alone.

CONCLUSIONS

Nitrogen mustard induces dose-dependent skin injury, while metformin reduces inflammation, apoptosis (TUNEL), and HMGB1-associated damage, highlighting its therapeutic potential in an ex vivo human-skin model.